Mariia S. Kirillova

Total Syntheses of Novel Cannabinoids and Lundurines A−C with a Golden Touch

DOCTORAL THESIS

Supervised by Prof. Antonio M. Echavarren

ICIQ – Institut Català d'Investigació Química

UNIVERSITAT ROVIRA I VIRGILI

Tarragona 2016

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I STATE that the present study, entitled *'Total Syntheses of Novel Cannabinoids and Lundurines A−C with a Golden Touch'*, presented by Mariia S. Kirillova to receive the degree of Doctor, has been carried out under my supervision at the Institut Català d'Investigació Química (ICIQ).

Tarragona, May the 20th 2016

Doctoral Thesis Supervisor

Prof. Antonio M. Echavarren Pablos

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Моим любимым родителям

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"Ever tried. Ever failed. No matter.
Try again. Fail again. Fail better."

Samuel Beckett

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I would like to thank all the members of the Echavarren group, the former ones as well as the current ones for their support. I wanna say a joint thanks to all my labmates that contributed in giving this laboratory its friendly atmosphere.

Especial thanks to all the members of the Lundurine team: Michael E. Muratore and Ruth Dorel for the pleasant and successful collaboration. Together we made it possible!

Also I would like to thank Javier Carreras for his valuable contribution in the project and resolving the anhydrocannabimovone mystery.

I want to address my special thanks to people who helped me to prepare this manuscript. THANK YOU Michael, Brayan and Fedor for proofreading this thesis, for your useful suggestions, helpful discussions and interesting questions.

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TOTAL SYNTHESES OF NOVEL CANNABINOIDS AND LUNDURINES A¿C WITH A GOLDEN TOUCH
Mariia Kirillova

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Mariia Kirillova

At the moment of writing this manuscript, the results presented herein have been published in:

1. **Concise Total Synthesis of Lundurines A–C Enabled by Gold Catalysis and a Homodienyl Retro-Ene / Ene Isomerization**
   Kirillova, M. S.; Muratore, M. E.; Dorel, R.; Echavarren, A. M. *J. Am. Chem. Soc.* **2016**, *138*, 3671−3674.

2. **Synthesis of (−)-Cannabimovone and Structural Reassignment of Anhydrocannabimovone through Gold(I)-Catalyzed Cycloisomerization**
   Carreras, J.; Kirillova, M. S.; Echavarren, A. M. *Angew. Chem. Int. Ed.* **2016**, DOI: 10.1002/anie.201601834.

Table of Contents

Prologue

The manuscript of this Doctoral Thesis has been divided into three main parts: a general introduction into gold(I)-catalysis as a powerful tool for the total synthesis of natural products followed by two research chapters. Each chapter consists of five sections: an introduction on the research topic, the objectives, and a discussion on the obtained results, ending with the conclusions and the experimental part.

The general introduction provides an overview on the application of gold catalysis in target-oriented synthesis and will be highlighted in several topics: the aldol reaction of isocyanoacetates and aldehydes, addition of heteronucleophiles to alkynes and allenes, gold catalyzed reactions of alkene-alkyne, transformations of propargyl carboxylate in the presence of gold catalysts, hydroarylation of alkynes and allenes, oxidation reactions, tandem-domino reactions, synthesis of (hetero)arenes, glycosylation, gold catalyzed allylic substitution of free alcohols and some other transformations catalyzed by gold salts.

The first chapter titled 'Synthesis of (−)-Cannabimovone and Structural Reassignment of Anhydrocannabimovone' describes the first total synthesis of novel cannabinoids cannabimovone and anhydrocannabimovone. The key step of this enantioselective synthesis is a fully diastereoselective gold(I)-catalyzed cyclization that efficiently forms a five member ring. A part of these results has been published in *Angew. Chem. Int. Ed.* **2016**, DOI: 10.1002/anie.201601834**.** This project was performed in collaboration with Dr. Javier Carreras.

The second chapter titled 'Total Synthesis of Lundurine A-C' describes an elaboration of a unified approach towards the synthesis of the natural products lundurines A–C. We developed an efficient method for the generation of the C20 stereocenter *via* a tandem condensation / lactamization / [3,3]-sigmatropic Claisen rearrangement. In addition, we applied gold(I)-catalyzed alkyne hydroarylation and a new intramolecular cyclopropanation of indoles by the formation of a pyrazoline, in order to construct the skeleton of the natural products. A remarkably facile olefin migration through a vinylcyclopropane retro-ene / ene rearrangement was found and applied to the synthesis. Finally, the challenging late stage functionalization was achieved by thiolation / *C*-sulfinylation-elimination and either oxidation or reduction strategy. A part of these results has been published in *J. Am. Chem. Soc.* **2016**, 138, 3671−3674. This project was performed in collaboration with Dr. Michael E. Muratore and Ruth Dorel.

List of Abbreviations and Acronyms

In this manuscript, the abbreviations and acronyms most commonly used in organic and organometallic chemistry have been used following the recommendations from "Guidelines for authors" of *Journal of Organic Chemistry*.

Abbreviations and acronyms used in this manuscript are referenced in the list below:

acac	Acetylacetonate anion
Alloc	Allyloxycarbonyl
BAr_4^{F-}	Tetrakis[3,5-bis(trifluoromethyl)phenylborate]
BSTFA	*N,O*-Bis(trimethylsilyl)trifluoroacetamide
m-CPBA	*meta*-Chloroperoxybenzoic acid
CSA	Camphorsulfonic acid
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DFT	Density functional theory
DIBAL-H	Diisobutylaluminium hydride
DIPEA	*N,N*-Diisopropylethylamine
DMF	Dimethylformamide
(*R*)-DM-SEGPHOS	(*R*)-(+)-5,5′−Bis[di(3,5-xylyl)phosphino]-4,4′-bi-1,3-benzodioxole, [(4*R*)-(4,4′-bi-1,3-benzodioxole)-5,5′-diyl]bis[bis(3,5-dimethylphenyl)phosphine]
DMAP	4-Dimethylaminopyridine
DMP	Dess–Martin periodinane
DMSO	Dimethyl sulfoxide
s-DOSP	Tetrakis[(*S*)-(-)-*N*-(*p*-dodecylphenylsulfonyl)prolinate]
dr	Diastereomeric ratio
DMS	Dimethyl sulfide
EDC	*N*-(3-Dimethylaminopropyl)-*N*′-ethylcarbodiimide
ee	Enantiomeric excess
er	Enantiomeric ratio
equiv	Equivalents
JohnPhos	(2-Biphenyl)di-*tert*-butylphosphine
GC	Gas chromatography
h	Hour / hours
HMDS	Bis(trimethylsilyl)amine

HMPA	Hexamethylphosphoramide
IBX	2-Iodoxybenzoic acid
HPLC	High-performance liquid chromatography
Im	Imidazole
IPr	1,3-Bis(2,4,6-trimethylphenyl)imidazole-2-ylidene
L	Ligand
LDA	Lithium diisopropylamide
min	Minutes
mix	Mixture
MS	Molecular sieves
MW	Microwave
ND	Not detected
NHC	*N*-heterocyclic
NIS	*N*-Iodosuccinimide
NMO	4-Methylmorpholine N-oxide
Ns	Nitrobenzenesulfonyl
NTf_2^-	Bis(trifluoromethyl)imidate
Nu	Nucleophile
OTf^-	Triflate
PCC	Pyridinium chlorochromate
PMP	1,2,2,6,6-Pentamethylpiperidine
PTSA	*para*-Toluenesulfonic acid
Py	Pyridine
SM	Starting material
TBAF	Tetra-*n*-butylammonium fluoride
TBS	*tert*-Butyldimethylsilyl
TEA	Triethylamine
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
TIPS	Triisopropylsilyl
TMEDA	Tetramethylethylenediamine
TMS	Trimethylsilyl
$TpBr^3$	hydrotris(3,4,5-tribromo)-pyrazolylborate

Ts	Tosyl
XPhos	2-Dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl

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Mariia Kirillova

General Introduction. Gold In Total Synthesis.

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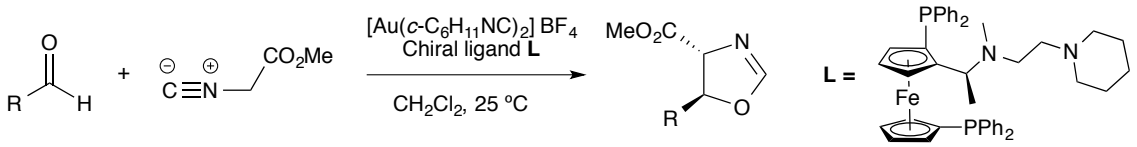
Mariia Kirillova

General Introduction. Gold In Total Synthesis.

The serendipitous synthesis of urea[1] reported in 1828 by Friedrich Wöhler is considered the beginning of organic chemistry as an independent discipline, although John Davy had previously synthesized urea in 1811 before Wöhler himself did it in 1824. It was only after four years of investigation that Wöhler succeeded in identifying that the colorless, odorless, water-soluble solid that he isolated was urea and not ammonium cyanate, his intended target.

During the next couple of centuries, organic chemistry as a discipline has expanded tremendously. The number of research reports on the methodology towards new transformations as well as the total syntheses of challenging targets has been increasing every year. Transition metal catalysis played an important role in the evolution of this field and shortly before the turn of the millennium, gold chemistry became a hot topic in the research in catalysis.

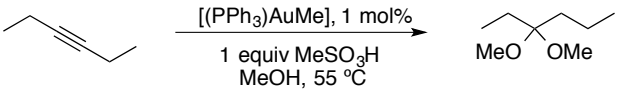
In 1986, Hayashi and Ito described the first application of chiral gold complexes for the asymmetric aldol reaction of aldehydes with isocyanides[2] (Scheme 1) and applied this methodology to the synthesis of *threo*- and *erythro*-sphingosines, amino alcohols with an unsaturated hydrocarbon chain.[3]



Scheme 1. Ito-Hayashi asymmetric aldol reaction.

A decade later, Teles reported the formation of acetals *via* addition of alcohols to alkynes catalyzed by gold(I) complexes,[4] (Scheme 2) while Fukuda and Utimoto showed that gold is very reactive catalysts for the addition of *O*-,*N*-nucleophiles to alkynes and alkenes.[5]

(1) Wöhler, F. *Ann. Phys. Chem* **1828**, *12*, 253–256.
(2) Ito, Y.; Sawamura, M.; Hayashi, T. *J. Am. Chem. Soc.* **1986**, *108*, 6405–6406.
(3) Ito, Y.; Sawamura, M.; Hayashi, T. *Tetrahedron Lett.* **1988**, *29*, 239–240.
(4) Teles, H.; Brode, S.; Chabanas, M. *Angew. Chem. Int. Ed.* **1998**, *37*, 1415–1418.
(5) (a) Fukuda, Y.; Utimoto, K. *J. Org. Chem.* **1991**, *56*, 3729–3731. (b) Fukuda, Y.; Utimoto, K. *Bull. Chem. Soc. Jpn.* **1991**, *64*, 2013–2015. (c) Fukuda, Y.; Utimoto, K. *Synthesis* **1991**, 975–978.

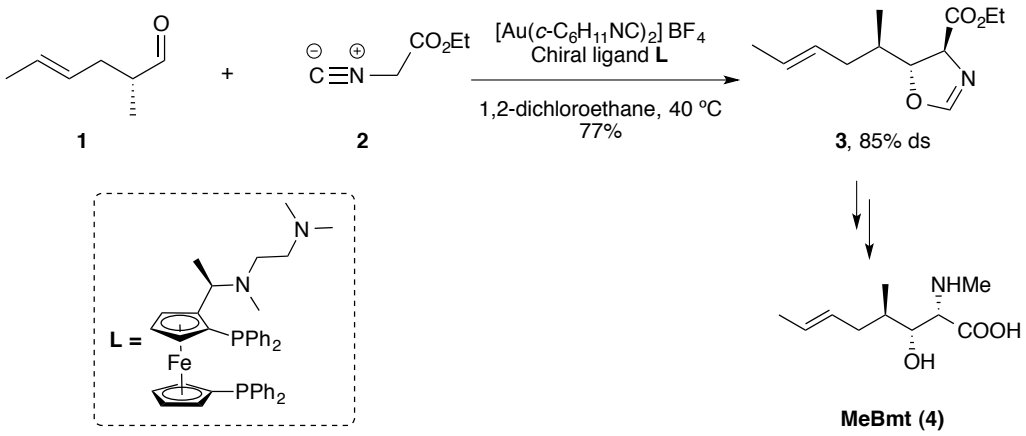


Scheme 2. Addition of alcohols to alkynes catalyzed by a gold(I) complex.

All these discoveries inaugurated a new branch of noble metal homogeneous catalysis. The initial rise of interest in the field of developing new transformations using gold complexes[6] and the increasing number of examples of the employment of gold catalysis to generate architecturally challenging targets indicates that gold catalysis is becoming a useful tool in the total synthesis of natural products.[7]

1. Aldol reaction of isocyanoacetates and aldehydes

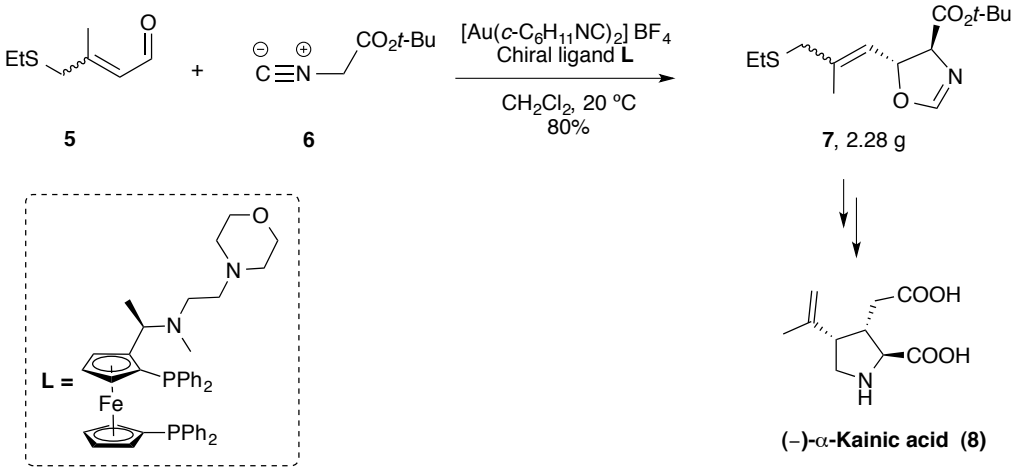
The gold-catalyzed asymmetric aldol reaction of aldehydes with isocyanides, developed by Ito and Hayashi, was used as a key step in the synthesis of MeBmt **4** (Scheme 3; MeBmt = (2*S*,3*R*,4*R*,6*E*)-3-hydroxy-4-methyl-2-(methylamino)oct-6-enoic acid). [8] Dihydro-1,3-oxazole **3** (8 : 1 *dr*) was obtained from chiral aldehyde **1** in the presence of a gold(I) / chiral ferrocenylphosphine system. Remarkably, a high level of diastereoselectivity was achieved by catalyst induction and only a weak effect of double stereodifferentiation was observed. In a few additional steps, 1,3-oxazoline **3** was converted into MeBmt (**4**), one of the amino acids constitutive of cyclosporin. This synthesis could be considered as one of the earliest examples of the application of homogeneous gold(I) catalysis in total synthesis.



Scheme 3. Asymmetric synthesis of MeBmt.

(6) Dorel, R.; Echavarren, A. M. *Chem. Rev.* **2015**, *115*, 9028–9072.
(7) Pflästerer, D.; Hashmi, A. S. K. *Chem. Soc. Rev*. **2016**, *45*, 1331−1367.
(8) Togni, A; Pastor, S. D.; Rihs, G. *Helv. Chim. Acta* **1989**, *72*, 1471–1478.

The efficiency of this elegant transformation was demonstrated once more in the context of the total synthesis of (−)-α-kainic acid **8** (Scheme 4).[9] The desired oxazoline **7** was obtained in good yield as a *ca* 3 : 1 mixture of *E* / *Z* isomers. The gold(I) / ferrocenylphosphine system showed remarkable tolerance to the thioether substituent and potential for multi-gram scale synthesis with low catalyst loading (1 mol %).



Scheme 4. Total synthesis of (−)-α-kainic acid.

2. Addition of heteronucleophiles to alkynes and allenes

2.1 O-Nucleophiles

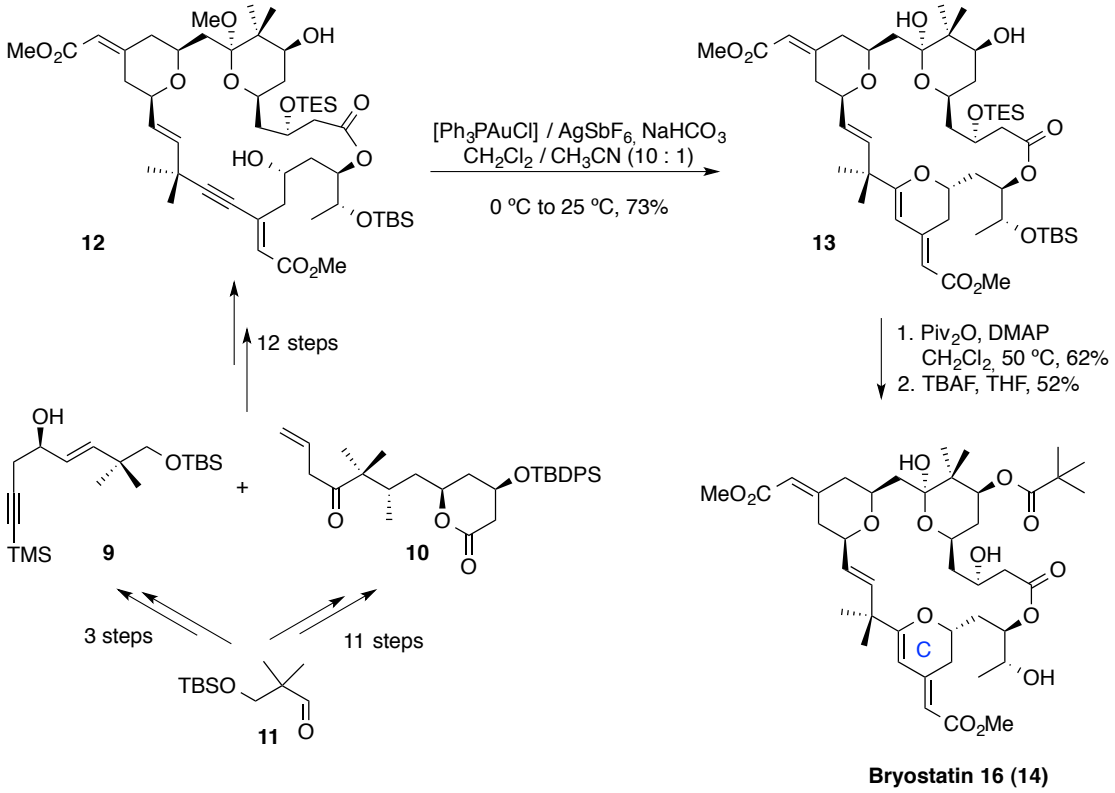
2.1.1 Hydroalkoxylation of alkynes

The gold-catalyzed hydroalkoxylation of alkynes found applications in the field of natural product synthesis. The utility of this transformation for the generation oxygen-containing heterocycles was demonstrated in the synthesis of (+)-cephalostatin 1 by Shair's group, in which the dihydrofuran ring was obtained by gold(I)-catalyzed *5-endo-dig* cyclization.[10] Other instances are found in the Fürstner's syntheses of (−)-polycavernoside A[11] and spirastrellolide F,[12] wherein the desired dihydropyrane moieties were assembled using cationic JohnPhos gold complex.

An interesting example of cyclic enol ether formation *via 6-endo-dig* cyclization is presented in the synthesis of bryostatin 16 (**14**) developed by Trost *et al.* (Scheme

(9) Bachi, M. D.; Melman, A. *J. Org. Chem.* **1997**, *62*, 1896–1898.
(10) Fortner, K. C.; Kato, D.; Tanaka, Y.; Shair, M. D. *J. Am. Chem. Soc.* **2010**, *132*, 275–280.
(11) Brewitz, L.; Llaveria, J.; Yada, A.; Fürstner, A. *Chem. Eur. J.* **2013**, *19*, 4532–4537.
(12) Benson, S.; Collin, M.-P.; Arlt, A.; Gabor, B.; Goddard, R.; Fürstner, A. *Angew. Chem. Int. Ed.* **2011**, *50*, 8739−8744.

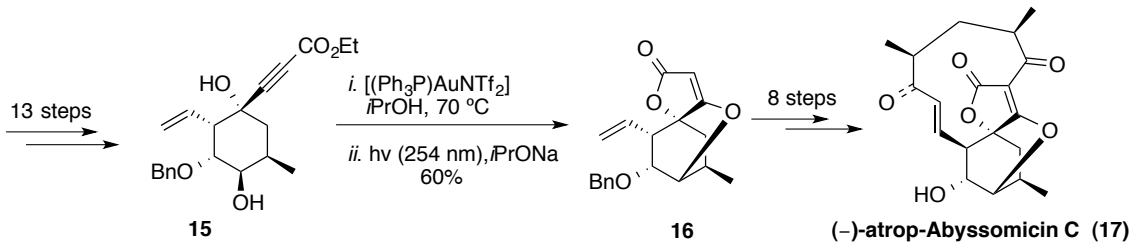
5).[13,14] A late stage palladium-catalyzed *6-endo-dig* cyclization of **12** to generate the C ring of bryostatin 16 showed only modest selectivity. However, when a cationic gold complex prepared from [(PPh_3)AuCl] and $AgSbF_6$ was used as the catalyst, the formation of the acid-sensitive dihydropyran **13** was achieved in 73% yield in the presence of $NaHCO_3$ as the buffer. The esterification under forcing conditions followed by the cleavage of silyl ethers provided the natural product.



Scheme 5. Total synthesis of bryostatin 16.

A *6-endo-dig* cyclization was employed to provide key intermediate **16** in the synthesis of (−)-atrop-abyssomicin C **17**, for which an intramolecular hetero-Michael addition strategy failed (Scheme 6).[15] Heating alkynol **15** with [(PPh_3)$AuNTf_2$] followed by UV-irradiation in the presence of sodium isopropoxide provided the desired bridged bicycle **16** in 60% overall yield. (−)-atrop-abyssomicin C **17** was obtained from key intermediate **16** in 8 additional steps.

(13) Trost, B. M.; Dong, G. *Nature* **2008**, *456*, 485–488.
(14) Trost, B. M.; Dong, G. *J. Am. Chem. Soc.* **2010**, *132*, 16403–16416.
(15) Bihelovic, F.; Siacic, R. N. *Angew. Chem. Int. Ed.* **2012**, *51*, 5687–5691.



Scheme 6. Total synthesis of (−)-atrop-abyssomicin C.

In the formal total synthesis of kendomycin accomplished by Fürstner and co-workers, gold(I) complex [(JohnPhos)AuOTs] triggered the addition of phenol to an alkyne which led to the formation of the required benzofuran, whereas $PtCl_2$ proved to be inefficient. This transformation delivered previously synthesized intermediates and completed the formal total synthesis of kendomycin.[16]

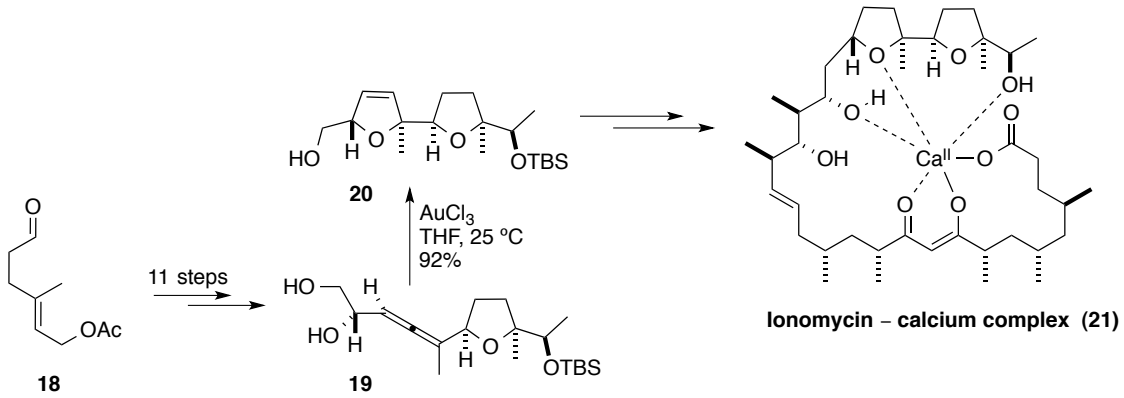
A gold-catalyzed hydration of alkynes was used in the synthesis of pterosines B and C[17] as well as in the synthesis of (±)-actinopolymorphol B by Sahoo *et al.*[18]

2.1.2 Hydroalkoxylation of allenes

Similarly, allenes can also undergo hydroalkoxylation in the presence of transition metal catalysts. Furthermore, several examples of the application of gold(I)-catalyzed hydroalkoxylation of allenes in total synthesis were disclosed.

Kocienski *et al.* accomplished the synthesis of ionomycin – calcium complex **21** employing a gold-catalyzed cycloisomerization of dihydroxyallene **19** to 2,5-dihydrofuran **20** as a key step (Scheme 7).[19] The use of a donor solvent, THF, and low catalyst loading minimized the decomposition and the cleavage of the TBS group.

(16) Hoffmeister, L.; Persich, P.; Fürstner, A. *Chem. Eur. J.* **2014**, *20*, 4396−4402.
(17) Wessig, P.; Teubner, J. *Synlett* **2006**, *10*, 1543−1546.
(18) Ghosh, N.; Nayak, S.; Sahoo, A. K. *J. Org. Chem.* **2011**, *76*, 500−511.
(19) Gao, Z.; Li, Y.; Cooksey, J. P.; Snaddon, T. N.; Schunk, S.; Viseux, E. M. E.; McAteer, S. M.; Kocienski, P. J. *Angew. Chem. Int. Ed.* **2009**, *48*, 5022–5025.

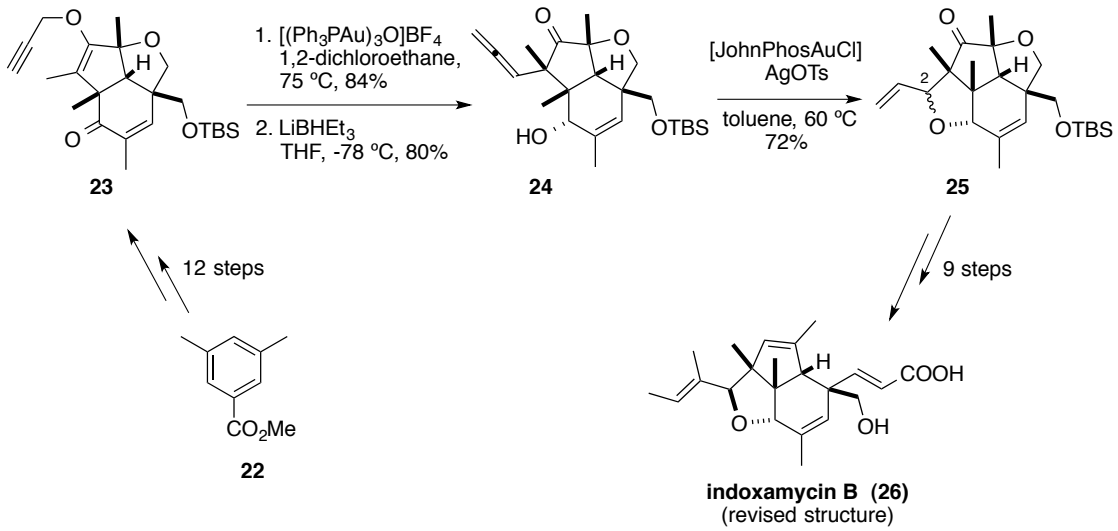


Scheme 7. Total synthesis of ionomycin – calcium complex.

An analogous transformation was employed by the group of Krause in the synthesis of β-carboline alkaloids (−)-isocyclocapitelline, (−)-isochrysotricine, [20] funanomycin derivatives[21] and bejarols.[22] One more example of the formation of functionalized dihydrofurans *via* gold-catalyzed hydroalkoxylation of allenes is found in the synthesis of jaspine B and its isomers by Reissig *et al*.[23]

The power and utility of gold catalysis was demonstrated by Carreira and co-workers in their synthesis of indoxamycin B **26** (Scheme 8).[24] The gold(I)-catalyzed Saucy−Marbet rearrangement of propargyl ether **23** followed by reduction of the most accessible ketone delivered allenol **24**. The gold(I)-catalyzed hydroalkoxylation of allene **24** provided tetracyclic intermediate **25** as a mixture of inseparable diastereomers at C2. Further elaboration of **25** resulted in the synthesis and reassignment of (±)-indoxamycin B stereochemical structure.

(20) (a) Volz, F.; Krause, N. *Org. Biomol. Chem.* **2007**, *5*, 1519–1521. (b) Volz, F.; Wadman, S. H.; Hoffmann-Röder, A.; Krause, N. *Tetrahedron* **2009**, *65*, 1902–1910.
(21) Erdsack, J.; Krause, N. *Synthesis* **2007**, *23*, 3741−3750.
(22) Sawama, Y.; Sawama, Y.; Krause, N. *Org. Biomol. Chem*. **2008**, *6*, 3573–3579.
(23) Schmidel, V. M.; Stefani, S.; Reissig, H.-U. *Beilstein J. Org. Chem.* **2013**, *9*, 2564–2569.
(24) Jeker, O. F.; Carreira, E. M. *Angew. Chem. Int. Ed.* **2012**, *51*, 3474–3477.



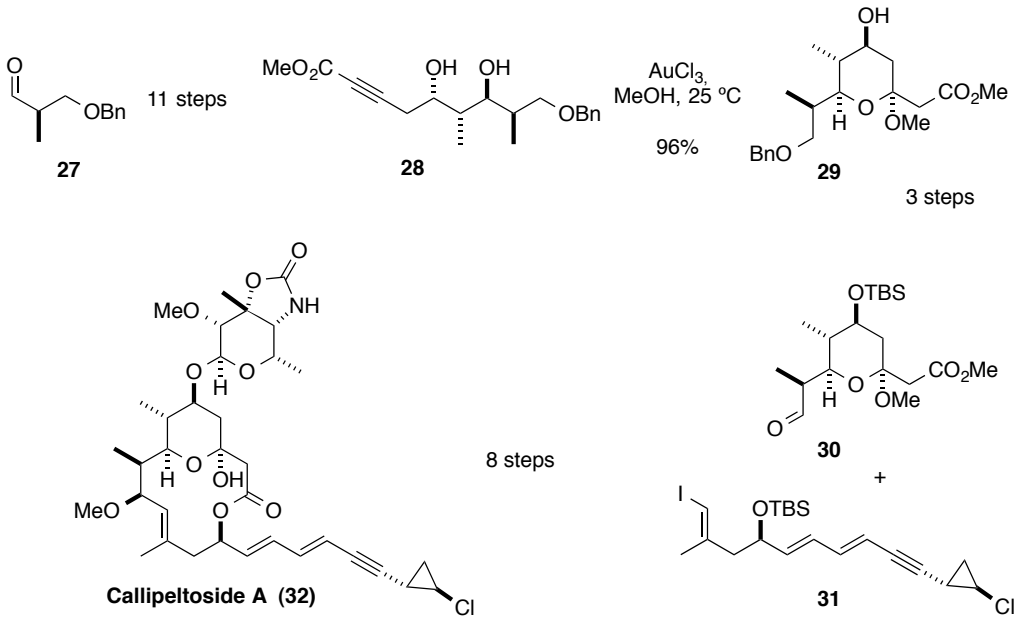
Scheme 8. Total synthesis of indoxamycin B.

2.1.3 Ketalization

A gold-catalyzed pyran formation was successfully applied to the synthesis of marine sponge metabolites callipeltosides A−C by Ley and co-workers (Scheme 9).[25] The elegant assembly of the desired tetrahydropyran **29** from alkyne **28** proceeded smoothly in the presence of gold(III) chloride in MeOH and provided **29** as a single diastereomer in excellent yield. The joining of the corresponding aldehyde **30** and vinyl iodide **31** followed by a few additional steps completed the synthesis of callipeltoside A. In addition, a similar transformation for the pyran formation was employed in the synthesis of (−)-hennoxazole.[26]

(25) Frost, J. R.; Pearson, C. M.; Snaddon, T. N.; Booth, R. A.; Ley, S. V. *Angew. Chem. Int. Ed.* **2012**, *51*, 9366–9371.
(26) Fernández, A.; Levine, Z. G.; Baumann, M.; Sulzer-Mossé, S.; Sparr, C.; Schläger, S.; Metzger, A.; Baxendale, I. R.; Ley, S. V. *Synlett* **2013**, *24*, 514–518.

General Introduction. Gold In Total Synthesis.

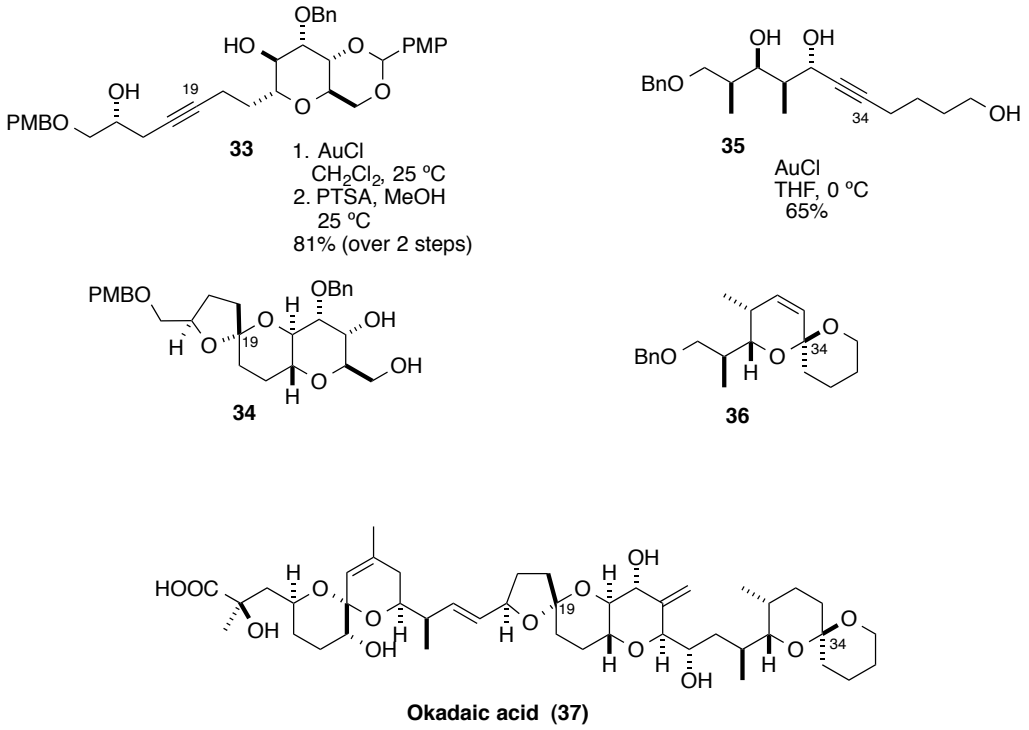


Scheme 9. Total synthesis of callipeltoside A.

The spiroketalization catalyzed by gold is another powerful method for the target-oriented synthesis of a wide variety of spiroketal-containing natural products. The advantages of the high activity and selectivity of gold as catalysts for the spiroketalization of alkynyldiols were clearly demonstrated in the total syntheses of (−)-ushikulide A,[27] cephalosporolide H epimers,[28] the A–D domain of azaspiracid,[29] and the formal synthesis of didemniserinolipid B.[30]

Two AuCl-catalyzed transformations were performed in the course of the formal total synthesis of okadaic acid by Forsyth *et al.*, which relied on the regioselective formation of two spiroketal fragments at C19 (**34**) and C34 (**36**) from the corresponding alkynyldiols **33** and **35** respectively (Scheme 10).[31] The construction of C19 spirotetrahydrofuran **34** was achieved by employing a catalytic amount of AuCl in dichloromethane. Remarkably, the partial acetonide cleavage did not affect the gold-catalyzed spirocyclization and the further deprotection delivered the desired diol **34** in good yield. The synthesis of the second fragment **36** was accomplished from 1,3-*anti* triol **35** that provided the required regioselectivity in the spirocyclization.

(27) Trost, B. M.; O'Boyle, B. M.; Hund, D. *J. Am. Chem. Soc.* **2009**, *131*, 15061–15074.
(28) Tlais, S. F.; Dudley, G. B. *Org. Lett.* **2010**, *12*, 4698−4701.
(29) Li, Y.; Zhou, F.; Forsyth, C. J. *Angew. Chem. Int. Ed.* **2007**, *46*, 279–282.
(30) Das, S.; Induvadana, B.; Ramana, C. V. *Tetrahedron* **2013**, *69*, 1881−1896.
(31) Fang, C.; Pang, Y.; Forsyth, C. J. *Org. Lett.* **2010**, *12*, 4528−4416.



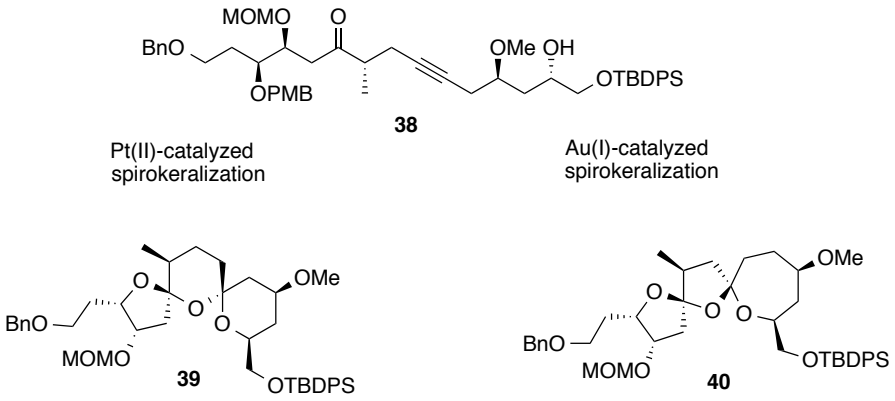
Scheme 10. Total synthesis of okadaic acid.

The benefits of this methodology were also demonstrated by Sarkar in the synthesis of xyloketals D, G and alboatrin,[32] as well as in Ramana's total synthesis of cephalosporolides E and F.[33] The gold(I)-catalyzed cycloisomerization of an alkynylpentaol was employed as a key step of the spirodienal A and spirangien A methyl ester syntheses,[34] although the desired spiroketal intermediate was isolated in moderate yield, this remains a good illustration of the utility gold catalysis even for highly complex systems.

A good exemplification of the opportunities that π-acid catalysts provide for spiroketal chemistry was reported by Smith and co-workers in their approach towards the construction of C26–C40 northern hemisphere of spirastrellolide B.[35] Two different tricyclic systems can be easily obtained from the same alkynol **38** by changing the transition metal catalyst triggering the alkyne functionalization (Scheme 11). The desired [5,6,6]-bisspiroketal **39** was obtained with $[Pt(CH_2CH_2)Cl_2]_2$, however the

(32) Panda, B.; Sarkar, T. K. *J. Org. Chem.* **2013**, *78*, 2413−2421.
(33) Kona, C. N.; Ramana, C. V. *Tetrahedron* **2014**, *70*, 3653–3656.
(34) Newton, S.; Carter, C. F.; Pearson, C. M.; de C. Alves, L.; Lange, H.; Thansandote, P.; Ley, S. V. *Angew. Chem. Int. Ed.* **2014**, *53*, 4915–4920.
(35) Wang, X.; Paxton, T. J.; Li, N.; Smith III, A. B. *Org. Lett.* **2012**, *14*, 3998–4001.

employment of gold(I)-catalyzed reaction resulted in the formation of the intriguing [5,5,7]-bisspiroketal analog **40**.

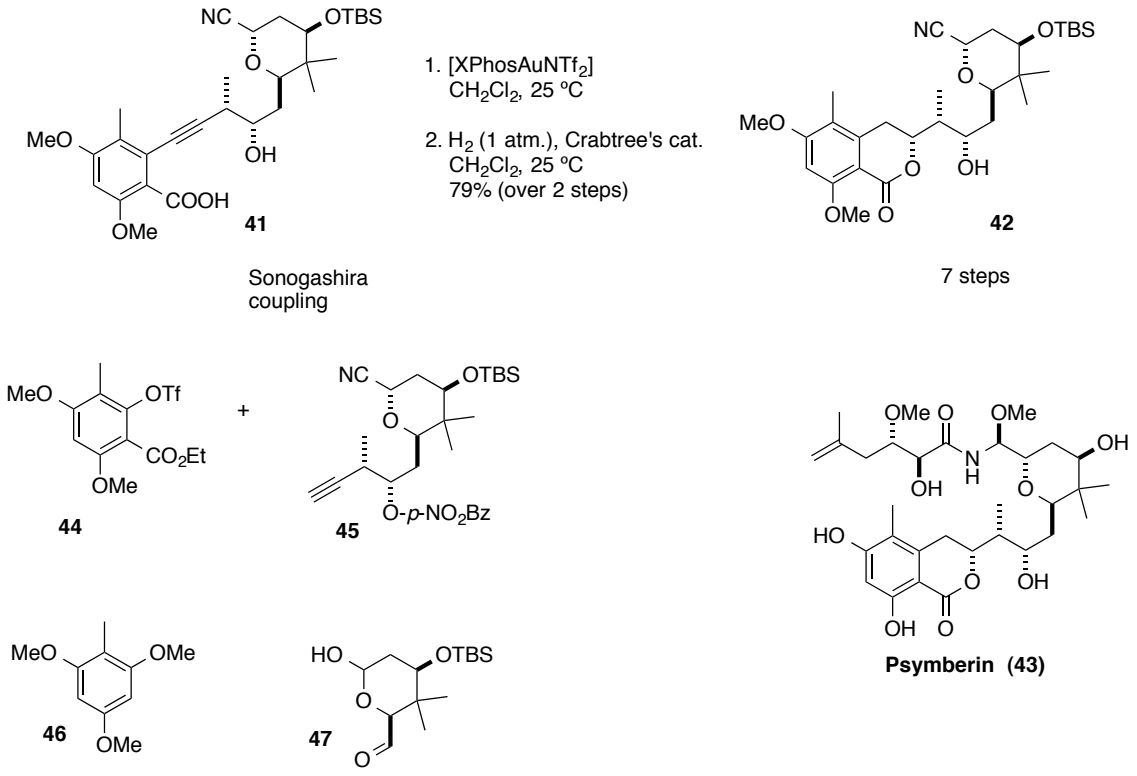


Scheme 11. The π-acid dependent outcome of a spiroketalization.

2.1.4 Hydrocarboxylation of alkynes and allenes

The gold-catalyzed hydrocarboxylation of alkynes and allenes has less precedent in the context of target-oriented synthesis. However a few interesting examples have been recently disclosed. The ability of carboxylic acid derivatives to add to alkynes in the presence of gold was effectively illustrated by De Brabander *et al*. in their synthesis of psymberin **43** (Scheme 12).[36] The formation of lactone **42** was problematic because of regioselectivity issues (*6-endo* vs *5-exo*) as well as the competing hydroalkoxylation of the alkyne. The employment of [XPhosAuNTf$_2$] as the catalyst provided the desired isocoumarin product **42** in 80% yield with up to > 95 : 5 selectivity (*6-endo* vs *5-exo*) while various cycloisomerization conditions (Brønsted acids, $InBr_3$, $AgSbF_6$, $[Pt(CH_2CH_2)Cl_2]_2$, $AuCl_3$) led to complex mixtures or poor selectivity. The synthesis of psymberin **43** from intermediate **42** was completed in 8 additional steps.

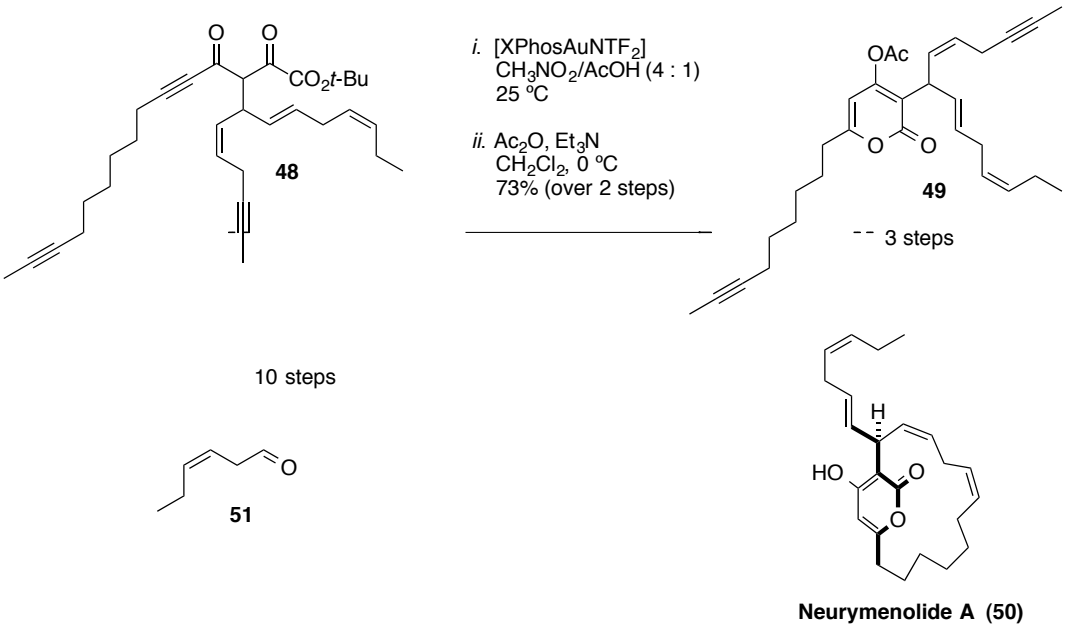
(36) Feng, Y.; Jiang, X.; De Brabander, J. K. *J. Am. Chem. Soc*. **2012**, *134*, 17083−17093.



Scheme 12. Total synthesis of psymberin.

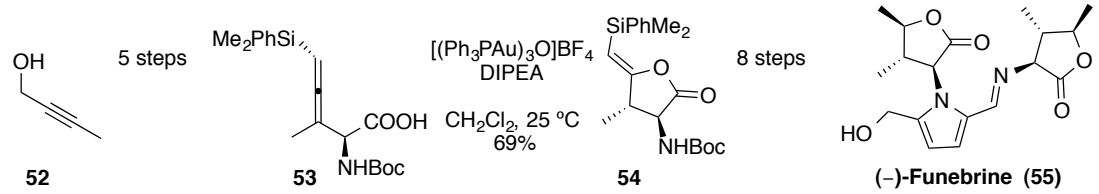
The utility of the gold-catalyzed hydrocarboxylation was also demonstrated in Fürstner's synthesis of neurymenolide A **50** (Scheme 13).[37] The use of bulky [XPhosAuNTf$_2$] and AcOH as the co-solvent, presumably to accelerate the protodeauration step, resulted in the formation of the required 4-hydroxy-2-pyrone followed by *in situ* acetylation, which was essential to suppress the fast isomerization of the alkene sidechains. The synthesis of neurymenolide A **50** was then accomplished in a few additional steps from pyrone **49**. A similar transformation was applied to the construction of a 2-alkoxy-4-pyrone by the same group in the course of an algal metabolite synthesis[38] and by Lee *et al.* for (+)-violapyrone C.[39]

(37) Chaladaj, W.; Corbet, M.; Fürstner, A. *Angew. Chem. Int. Ed*. **2012**, *51*, 6929–6933.
(38) Hoffmeister, L.; Fukuda, T.; Pototschnig, G.; Fürstner, A. *Chem. Eur. J.* **2015**, *21*, 4529–4533.
(39) Lee, J. S.; Shin, J.; Shin, H. J.; Lee, H.-S.; Lee, Y.-J.; Lee, H.-S.; Won, H. *Eur. J. Org. Chem.* **2014**, 4472−4476.



Scheme 13. Total synthesis of neurymenolide A.

In the case of allenes, the gold(I)-catalyzed hydrocarboxylation was employed by Ohfune and co-workers in the course of their synthesis of (−)-funebrine (Scheme 14).[40] The lactonization of allene **53** effected by a trinuclear gold complex delivered the desired γ-butyrolactone **54**. Diisopropylethylamine (20 mol %), an unusual additive, allowed to decrease the catalyst loading to 1 mol % without affecting the outcome of the reaction.



Scheme 14. Total synthesis of (−)-funebrine.

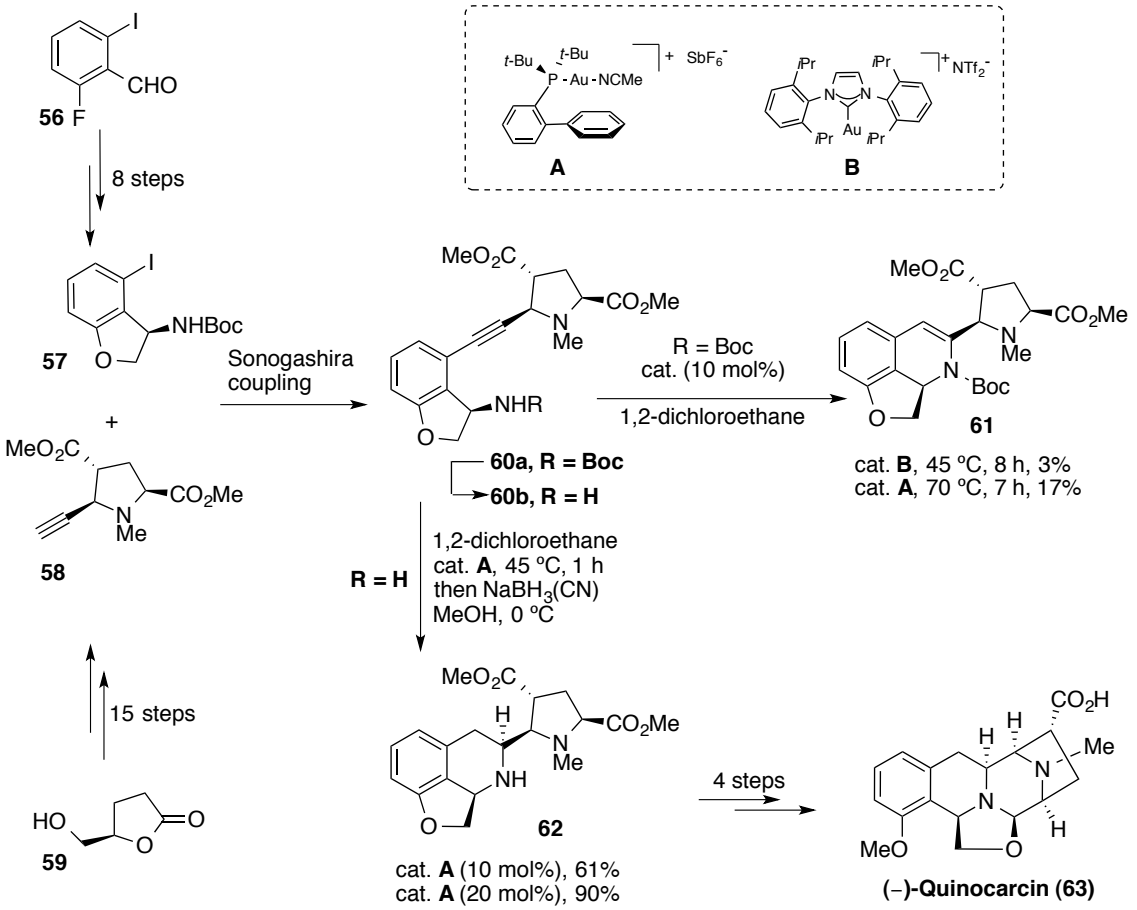
2.2. N-Nucleophiles

2.2.1 Hydroamination of alkynes

An alkyne hydroamination promoted by π-acid catalysts, such as gold, is a powerful tool for the generation of nitrogen containing heterocycles and complex architectures of natural products. The utility of this transformation in the field of target-oriented synthesis was demonstrated by the studies of Ohno and Fujii towards the synthesis of

(40) Okada, T.; Sakaguchi, K.; Shinada, T.; Ohfune, Y. *Tetrahedron Lett.* **2011**, *52*, 5744–5746.

(−)-quinocarcin **63** (Scheme 15).[41] The formation of dihydroisoquinoline fragment **61** was accomplished by gold(I)-catalyzed hydroamination of alkyne **60a**, although the enamine **61** was obtained in low yield, presumably as a result of the steric hindrance of the Boc group. The desired *6-endo-dig* cyclization triggered by JohnPhos cationic gold(I) complex proceeded efficiently for the free amine **60b**, providing the corresponding unstable enamine that was reduced *in situ* into its corresponding tetrahydroisoquinoline **62**. The synthesis of (−)-quinocarcin was completed in a few additional steps.



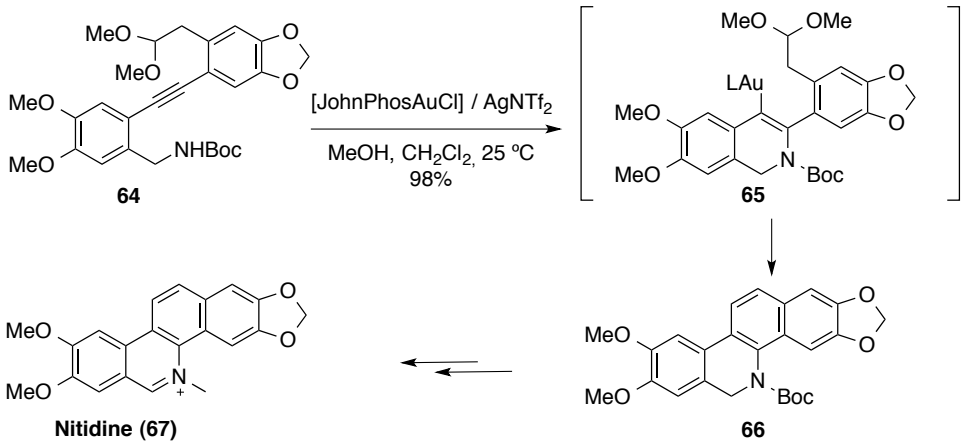
Scheme 15. Total synthesis of (−)-quinocarcin.

The gold(I)-catalyzed *6-endo-dig* cycloisomerization of alkynylamines was used as the key step in the total synthesis of piperidine alkaloids isosolepsin, isosolepsin A, (+)-241D[42] and (−)-epimyrtine[43] by Gouault *et al*. and andrachcinidine[44] by Floreancig.

(41) (a) Chiba, H.; Oishi, S.; Fujii, N.; Ohno, H. *Angew. Chem. Int. Ed.* **2012**, *51*, 9169–9172. (b) Chiba, H.; Sakai, Y.; Oishi, S.; Fujii, N.; Ohno, H. *Tetrahedron Lett.* **2012**, *53*, 6273–6276. (c) Chiba, H.; Sakai, Y.; Ohara, A.; Oishi, S.; Fujii, N.; Ohno, H. *Chem. Eur. J.* **2013**, *19*, 8875–8883.
(42) Gouault, N.; Le Roch, M.; de Campos Pinto, G.; David, M. *Org. Biomol. Chem.* **2012**, *10*, 5541−5546.

General Introduction. Gold In Total Synthesis.

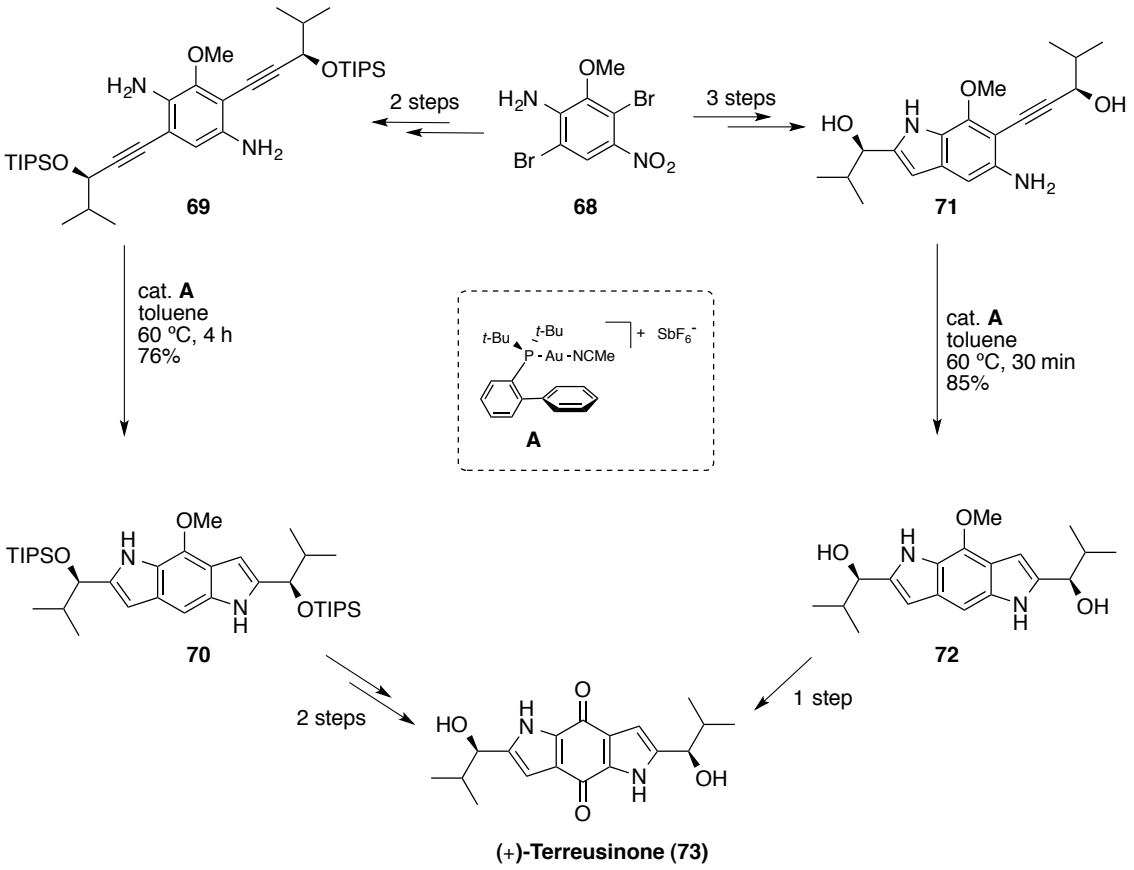
The formation of tetracyclic heterocycles from alkynyl carbamates bearing an enone or acetal was successfully applied to the formal total synthesis of nitidine (Scheme 16).[45] This single catalyst mediated a tandem cyclization consisting of a gold-catalyzed intramolecular hydroamination of alkyne **64** to form enecarbamate **65** that underwent a gold(I)-promoted intramolecular Mukaiyama-type aldol condensation, followed by aromatization through loss of methanol to furnish the corresponding polycyclic product **66**.



Scheme 16. Total synthesis of nitidine.

The gold-catalyzed hydroamination of alkynes found an application in the total synthesis of (+)-terreusinone **73** (Scheme 17).[46] The tricyclic core of the natural product can be achieved by two alternative strategies: the double hydroamination of diyne **69** or the hydroamination of alkynylindole **71**. The *5-endo-dig* hydroheterocyclization of alkynylamine **71** into pyrroloindoles **72** occurred smoothly in the presence of cationic JohnPhos gold(I) complex. Remarkably, the double hydroamination events for diyne **69** also took place very efficiently under identical conditions providing **70** in good yield. A straightforward functional group modification completed the synthesis of (+)-terreusinone.

(43) Trinh, T. T. H.; Nguyen, K. H.; de Aguiar Amaral, P.; Gouault, N. *Beilstein J. Org. Chem.* **2013**, *9*, 2042−2047.
(44) Jung, H. H.; Floreancig, P. E. *J. Org. Chem.* **2007**, *72*, 7359−7366.
(45) Enomoto, T.; Girard, A.-L.; Yasui, Y.; Takemoto, Y. *J. Org. Chem.* **2009**, *74*, 9158−9164.
(46) (a) Wang, C.; Sperry, J. *Org. Lett.* **2011**, *13*, 6444−6447. (b) Wang, C.; Sperry, J. *Synlett* **2012**, *23*, 1824−1828. (c) Wang, C.; Sperry, J. *Tetrahedron* **2013**, *69*, 4563–4577.



Scheme 17. Total synthesis of (+)-terreusinone.

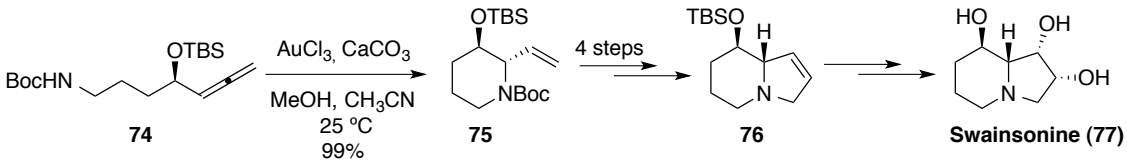
Another instance of indole formation *via* gold-catalyzed hydroamination of alkynes is presented in the total synthesis of (−)-mersicarpine.[47] A *7-exo-dig* cyclization of alkynylamine was developed by Funk and co-workers allowing the construction of the communesin ring system.[48]

2.2.2 Hydroamination of allenes

In contrast to the aforementioned hydroamination of alkynes, the hydroamination of allenes in target-oriented synthesis is uncommon. An example of this transformation used as a key step can be found in the formal synthesis of swainsonine **77** by Bates and Dewey (Scheme 18).[49] An extensive screening of conditions showed that the desired intramolecular hydroamination product **75** could be obtained in nearly quantitative yield employing $AuCl_3$. The addition of acetonitrile and calcium carbonate as additives were needed to solubilize and stabilize gold(III) chloride. Further elaboration of piperidine **75**

(47) Nakajima, R.; Ogino, T.; Yokoshima, S.; Fukuyama, T. *J. Am. Chem. Soc.* **2010**, *132*, 1236−1237.
(48) Crawley, S. L.; Funk, R. L. *Org. Lett.* **2016**, *8*, 3995−3998.
(49) Bates, R. W.; Dewey, M. R. *Org. Lett.* **2009**, *11*, 3706−3708.

provided the precedented indolizidine intermediate **76** and completed the formal total synthesis of swainsonine.



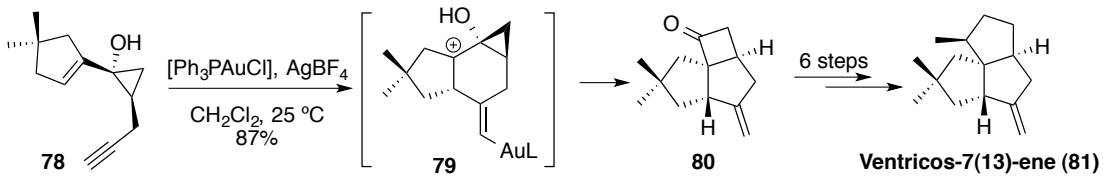
Scheme 18. Total synthesis of swainsonine.

The same group accomplished the formal synthesis of porantheridine that also utilized an allene hydroamination as a key step.[50] However, in this case the best results were obtained using silver(I) tetrafluoroborate, while gold salts only provided moderate diastereoselectivity.

3. Gold-catalyzed reactions of alkene-alkyne

3.1.1 Enyne cycloisomerization

The transition metal-catalyzed cycloisomerization of 1,n-enynes have been widely used in natural product synthesis due to its ability to significantly increase molecular complexity in a single step. The total synthesis of (±)-ventricos-7(13)-ene **81** nicely demonstrated the utility of a gold-catalyzed enyne cycloisomerization for the rapid construction of a complex polycyclic ring system (Scheme 19).[51] The formation of cyclopropylmethyl cation **79** *via 6-endo-dig* cyclization of vinyl cyclopropanol **78**, followed by a semipinacol rearrangement, delivered the required cyclobutanone **80** as a single diastereomer. The elaboration of the intermediate **80** completed the synthesis of the angular triquinane ventricosene in 6 additional steps.

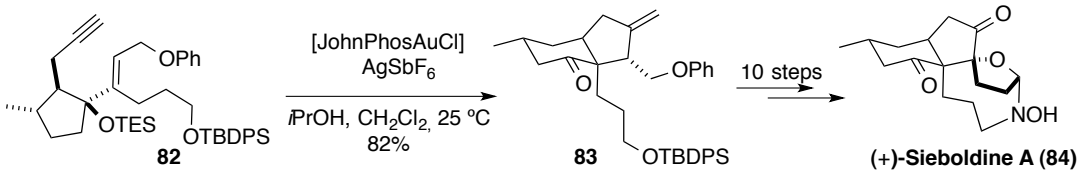


Scheme 19. Total synthesis of (±)-ventricos-7(13)-ene.

The total synthesis of (+)-sieboldine A **84** by Overman *et al*. is an illustration of the potential advantages of the 1,6-enyne cyclization for target-oriented synthesis (Scheme

(50) Bates, R. W.; Lu, Y. *J. Org. Chem.* **2009**, *74*, 9460–9465.
(51) Sethofer, S. G.; Staben, S. T.; Hung, O. Y.; Toste, F. D. *Org. Lett.* **2008**, *10*, 4315−4318.

20).[52] The pinacol-terminated cyclization cascade catalyzed by a gold(I) complex allowed to convert alkyne **82** into the key *cis*-hydrindanone intermediate **83** needed for the total synthesis of (+)-sieboldine A, which was ultimately accomplished in 10 additional steps.



Scheme 20. Total synthesis of (+)-sieboldine A.

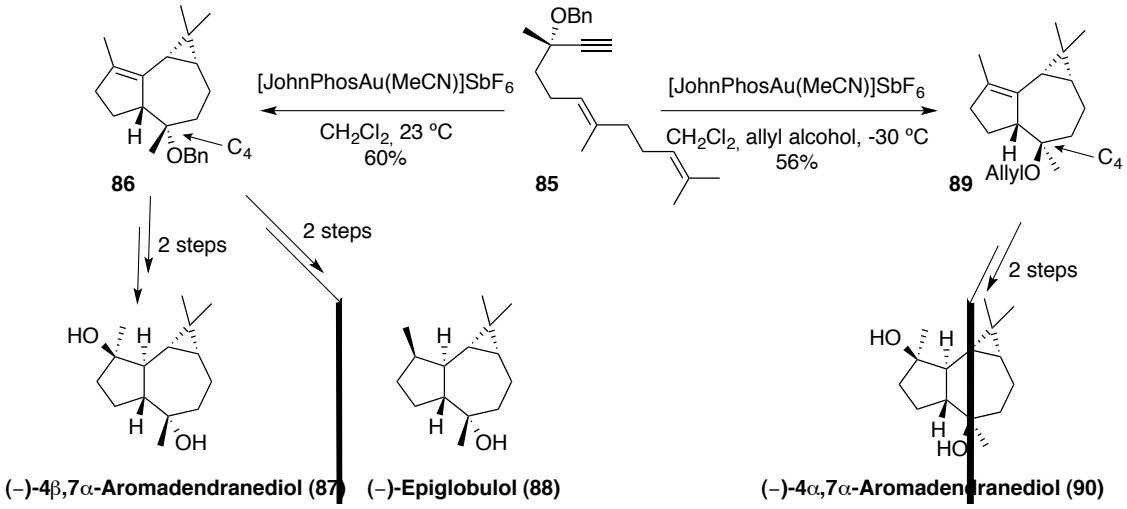
A highly efficient and enantioselective cycloisomerization of enynes was applied to the synthesis of antidepressive drug candidate GSK1360707 by the group of Fürstner.[53] The key step of the synthesis of the tricyclic core of stemonamine alkaloids and the formal synthesis of (±)-stemonamine[54] involved a one-pot gold(I)-catalyzed cycloisomerization and a $SnCl_4$-promoted Schmidt rearrangement. The synthesis of the tricyclic core of crotobarin and crotogoudin[55] by Jia and coworkers is another illustration of the power of enyne cyclization catalyzed by gold(I) for assembling polycyclic structures.

3.1.2 Enyne cycloisomerization with addition of nucleophiles

The total syntheses of the three representative aromadendranes (−)-4α,7α-aromadendranediol **87**, (−)-epiglobulol **88** and (−)-4β,7α-aromadendranediol **90** have been accomplished though the stereodivergent gold(I)-catalyzed cyclization cascade of the easily accessible dienyne **85** (Scheme 21).[56] This transformation consists of a cyclization, the 1,5-migration of the propargylic ether or the attack of an external nucleophile on the cyclopropyl gold carbene intermediate, and finally an intermolecular cyclopropanation. As a result, the tricyclic structures of **86** and **89** decorated with four new stereogenic centers were formed in a single step. Tricycle **86**, structurally related to epiglobulol, was obtained by exposing dienyne **85** to a cationic gold complex at room temperature. However the gold-catalyzed reaction of dienyne **85** performed at low temperature and in the presence of allyl alcohol as an external nucleophile led to the

(52) Canham, S., M.; France, D. J.; Overman, L. E. *J. Am. Chem. Soc*. **2010**, *132*, 7876−7877.
(53) Teller, H.; Fürstner, A. *Chem. Eur. J.* **2011**, *17*, 7764−7767.
(54) Kim, C.; Kang, S.; Rhee, Y. H. *J. Org. Chem.* **2014**, *79*, 11119−11124.
(55) Guo, Y.; Liu, Q.; Jia, Y. *Chem. Commun.* **2015**, *51*, 889−891.
(56) Carreras, J.; Livendahl, M.; McGonigal, P. R.; Echavarren, A. M. *Angew. Chem. Int. Ed.* **2014**, *53*, 4896–4899.

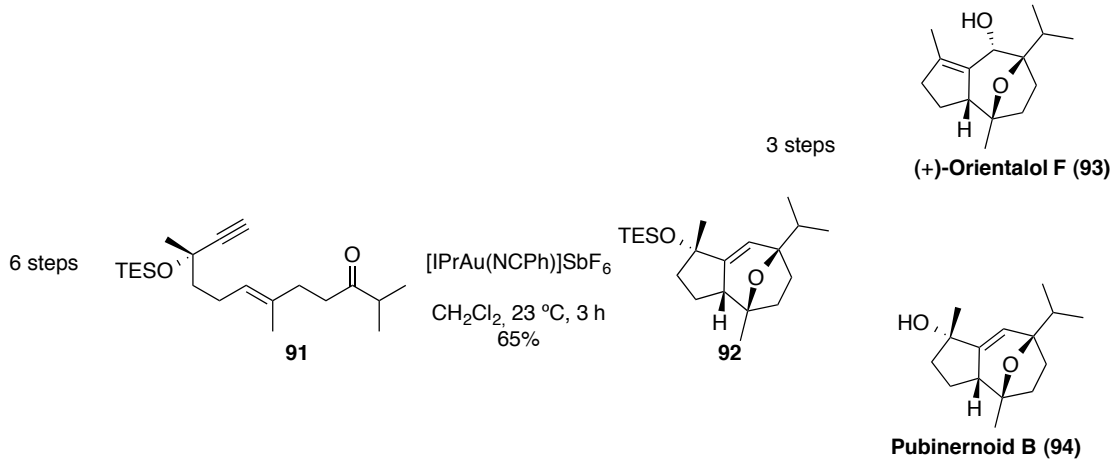
generation of tricycle **89** with the opposite configuration at C4. Two additional steps were required to convert each product of the gold(I)-catalyzed cyclization cascade into (−)-epiglobulol, (−)-4α,7α-aromadendranediol and (−)-4β,7α-aromadendranediol respectively.



Scheme 21. Total synthesis of (−)-epiglobulol, (−)-4α,7α-aromadendranediol and (−)-4β,7α-aromadendranediol.

The [2+2+2] alkyne / alkene / carbonyl gold(I)-catalyzed cycloaddition of 1,6-enynes bearing a carbonyl moiety[57] established by Echavarren *et al.* was applied in the total synthesis of (+)-orientalol **93** and pubinernoid B **94** (Scheme 22).[58] The cyclization of 1,6-enyne **91** followed by intramolecular attack of the carbonyl moiety resulted in the formation of the tricyclic skeleton **92** of the natural product. Notably, the carbonyl attack on the cyclopropyl gold carbene was faster than the 1,5-migration of the corresponding propargylic ether. The straightforward functional group modification of oxacycle **92** completed the syntheses of the targeted molecules.

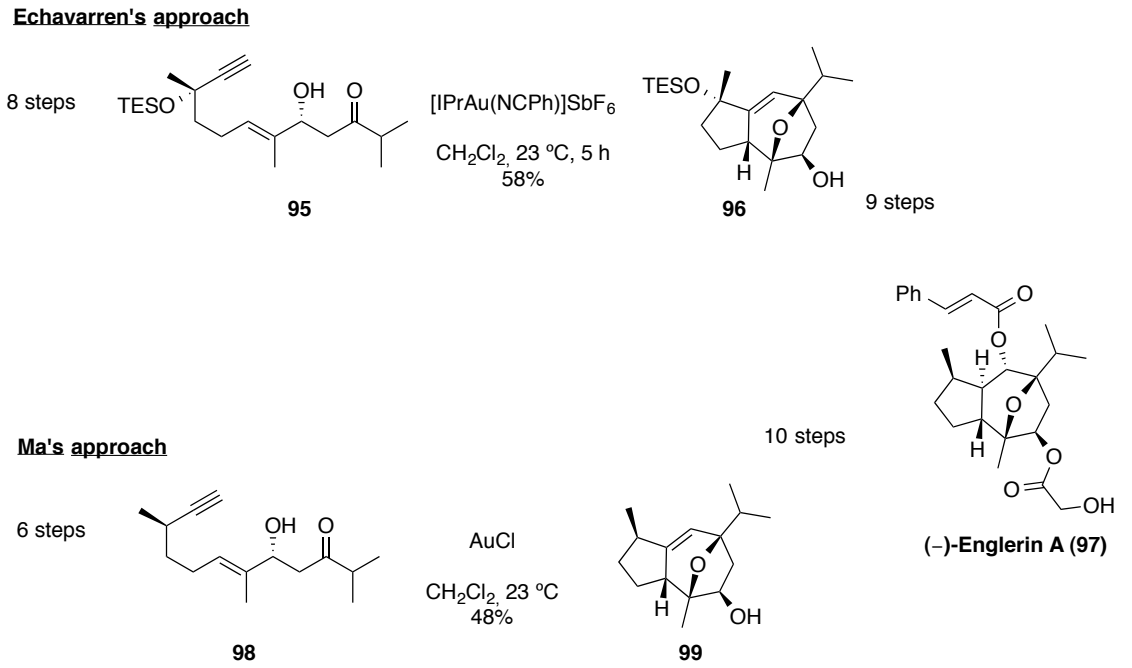
(57) (a) Jiménez-Núñez, E.; Claverie, C. K.; Nieto-Oberhuber, C.; Echavarren, A. M. *Angew. Chem. Int. Ed.* **2006**, *45*, 5452–5455. (b) Jiménez-Núñez, E.; Raducan, M.; Lauterbach, T.; Molawi, K.; Solorio, C. R.; Echavarren, A. M. *Angew. Chem. Int. Ed.* **2009**, *48*, 6152–6155.
(58) Jiménez-Núñez, E.; Molawi, K.; Echavarren, A. M. *Chem. Commun*. **2009**, *45*, 7327–7329.



Scheme 22. Total synthesis of (+)-orientalol F and pubinernoid B.

The same gold(I)-catalyzed domino process for the two C−C and one C−O bond formations was employed as a key step in two independent total syntheses of (−)-englerin A: the total synthesis of (−)-englerins A and B[59] by the group of Echavarren and the synthesis of (−)-englerin A developed by Ma and co-workers[60] (Scheme 23). The chiral linear chain precursors **95** and **98** bearing an unprotected alcohol group at the stereogenic allylic position were efficiently transformed into oxatricyclic intermediates **96** and **99** respectively. These intermediates were successfully converted into antitumor sesquiterpene (−)-englerin A **97** in 9 and 10 steps respectively. Although both groups used similar substrates in the gold-catalyzed step, their overall synthetic approaches to (−)-englerin A were very distinct.

(59) Molawi, K.; Delpont, N.; Echavarren, A. M. *Angew. Chem. Int. Ed.* **2010**, *49*, 3517–3519.
(60) Zhou, Q.; Chen, X.; Ma, D. *Angew. Chem. Int. Ed.* **2010**, *49*, 3513–3516.



Scheme 23. Total synthesis of (−)-englerin A by Echavarren and Ma.

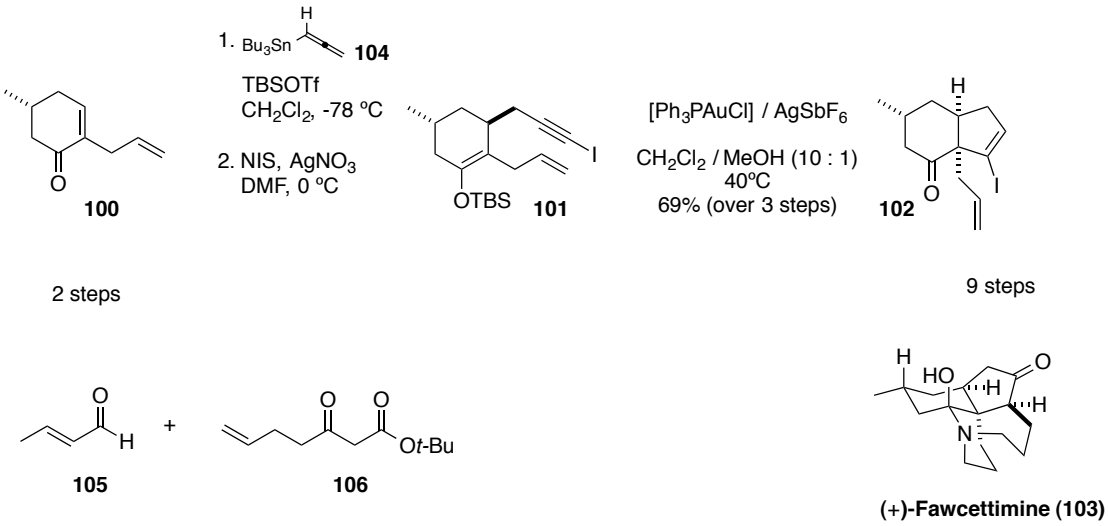
The gold-catalyzed cycloisomerization of 3-methoxy-1,6-enyne was used as a key step in the formal synthesis of clavukerin A by Rhee *et al*.[61] Two years later, the same group accomplished the formal synthesis of herbertene, α-herbertenol, β-herbertenol, and herbertenone *via* a gold(I)-mediated cycloisomerization of 5-siloxy-3-en-1-ynes.[62]

3.2 Carbocyclization of silyl enol ethers to alkynes. Conia-type reaction

The gold(I)-catalyzed cyclization of silyl enol ethers or enolizable 1,3-dicarbonyl compounds onto alkynes is an efficient method to construct polycycles containing quaternary stereocenters. This method has been widely used in the synthesis of architecturally challenging targets. The synthesis of (+)-lycopladine[63] accomplished by Toste and co-workers is the first examples of the application of a gold(I)-catalyzed cyclization of silylated enol in the context of the natural product synthesis. This reaction was also applied as a key step in the total synthesis of (+)-fawcettimine **103** (Scheme 24).[64] The conjugate propargylation of enone **100** with allenyltributylstannane **104** followed by iodination provided the desired silyl enol ether **101,** the desired precursor for the carbocyclization. The *5-endo-dig* cyclization of iodoalkyne **101** led to bicyclic

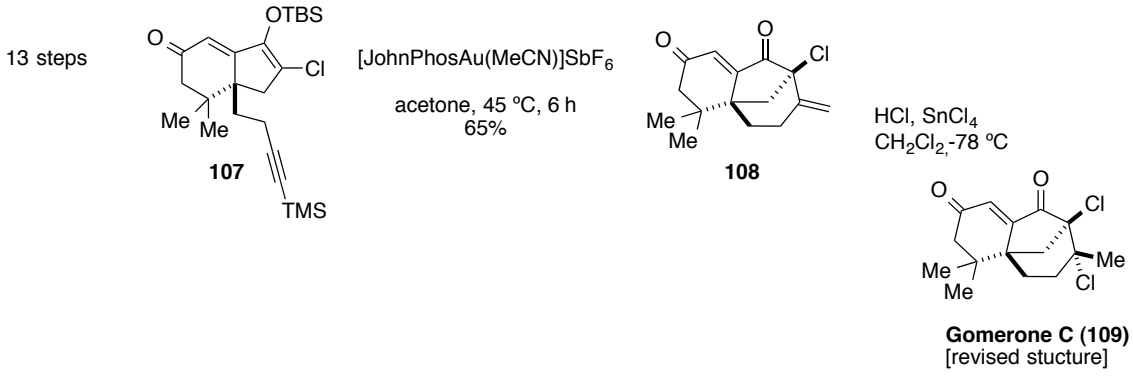
(61) Cheong, J. Y.; Rhee, Y. H. *Beilstein J. Org. Chem.* **2011**, *7*, 740−743.
(62) Jeong, J.; Lee, J.; Rhee, Y. H. *Bull. Korean Chem. Soc.* **2013**, *34*, 303−305.
(63) Staben, S. T.; Kennedy-Smith, J. J.; Huan, D.; Corkey, B. K.; LaLonde, R. L.; Toste, F. D. *Angew. Chem. Int. Ed.* **2006**, *45*, 5991−5994.
(64) Lunghu, X.; Kennedy-Smith, J. J.; Toste, F. D. *Angew. Chem. Int. Ed.* **2007**, *46*, 7671–7673.

derivative **102,** generating 2 stereocenters in a single step. Allyl-substituted vinyl iodide **102** was converted into (+)-fawcettimine in 9 additional steps.



Scheme 24. Total synthesis of (+)-fawcettimine.

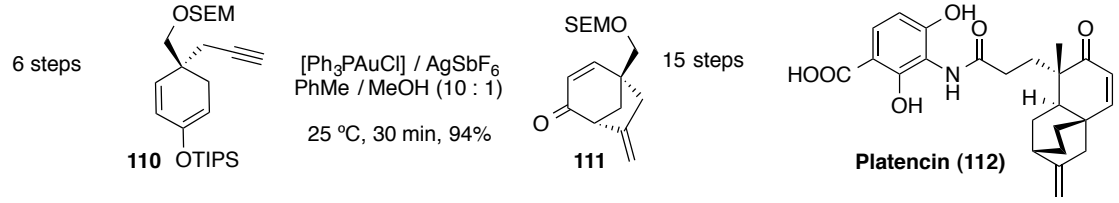
The concise total synthesis of chlorinated sesquiterpene (±)-gomerone C **109** is a good illustration of the efficiency of this synthetic tool (Scheme 25).[65] The late stage gold(I)-catalyzed cycloisomerization of 1,7-enyne **107** allowed constructing the tricyclic skeleton of the natural product and the concomitant generation of the exocyclic olefin required for further functional group modification. Chlorinated silyl enol ether **107** was successfully converted into the desired tricyclic ketone **108** by exposure it to [JohnPhosAu(NCMe)]SbF_6 in dry acetone, although partial alkyne desilylation was observed. The hydrochlorination of the exocyclic olefin completed this elegant synthesis of (±)-gomerone C. In addition, this work led to the revision of the originally assigned stereochemical structure of (±)-gomerone C and B.



Scheme 25. Total synthesis of (±)-gomerone C.

(65) Huwyler, N.; Carreira, E. M. *Angew. Chem. Int. Ed.* **2012**, *51*, 13066−13069.

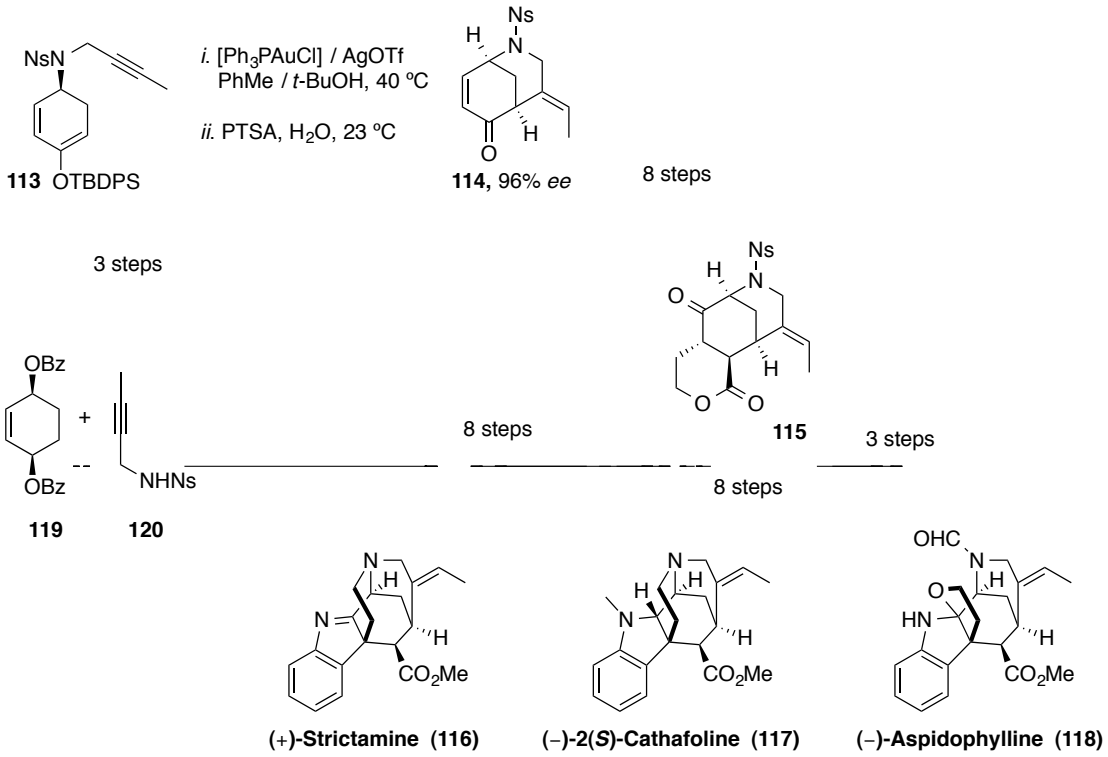
The total synthesis of the promising antibiotic platencin **112** is another example of the potential of the Conia-ene reaction for the synthesis of biologically active molecules (Scheme 26).[66] The gold(I)-catalyzed cyclization of acetylenic diene **110** led to the formation of the desired bicyclic enone **111** in excellent yield. Platencin was finally synthesized in 15 linear steps from enone **111**.



Scheme 26. Total synthesis of platencin.

The advantages of the gold(I)-promoted Conia-ene reaction of cyclic silyl enol ether for the generation of synthetically challenging natural alkaloid scaffolds was nicely highlighted in the total synthesis of daphenylline[67] and the tetracyclic core of daphnilongeranin B.[68] Another illustration of the utility of gold catalysis for target-oriented synthesis is found in the recently reported total syntheses of the akuammiline alkaloids (+)-strictamine **116**, (−)-2(*S*)-cathafoline **117** and (−)-aspidophylline A **118** (Scheme 27).[69] The alkyne precursor **113** for the key gold(I)-mediated cyclization was easily accessible in 3 steps from dibenzoate **119**. The Conia-ene reaction proceeded smoothly in the presence of a phosphine gold(I) complex and provided the required bicyclic ketone **114**. Further elaboration of this azabicyclic intermediate led to lactone **115**, the common precursor for (+)-strictamine **116**, (−)-2(*S*)-cathafoline **117** and (−)-aspidophylline A **118**. A Fischer indole synthesis followed by a late stage functional group modification completed the first total synthesis of two akuammiline alkaloids: (+)-strictamine and (−)-2(*S*)-cathafoline, as well as the first enantioselective total synthesis of (−)-aspidophylline A.

(66) Nicolaou, K. C.; Tria, G. S.; Edmonds, D. J. *Angew. Chem. Int. Ed.* **2008**, *47*, 1780−1783.
(67) Lu, Z.; Li, Y.; Deng, J.; Li, A. *Nat. Chem.* **2013**, *5*, 679–684.
(68) Xiong, X.; Li, Y.; Lu. Z.; Wan, M.; Deng, J.; Wu. S.; Shao, H.; Li, A. *Chem. Commun.* **2014**, *50*, 5294−5297.
(69) Moreno, J.; Picazo, E.; Morrill, L. A.; Smith, J. M.; Garg, N. K. *J. Am. Chem. Soc*. **2016**, *138*, 1162−1165.



Scheme 27. Total synthesis of akuammiline alkaloids.

The selectivity and reactivity of phosphine gold(I) complexes for the carbocyclization of cyclic silyl enol ethers to alkynes was brilliantly illustrated by the total synthesis of hyperforin and papuaforins A−C, and the formal synthesis of nemorosone.[70] The gold(I)-catalyzed *6-endo-dig* cyclization proceeded smoothly in spite of the sterically crowded environment, in the presence of [JohnPhosAu(MeCN)]SbF_6 and provided the desired bicyclic ketone in nearly quantitative yield on up to 10 g scale.

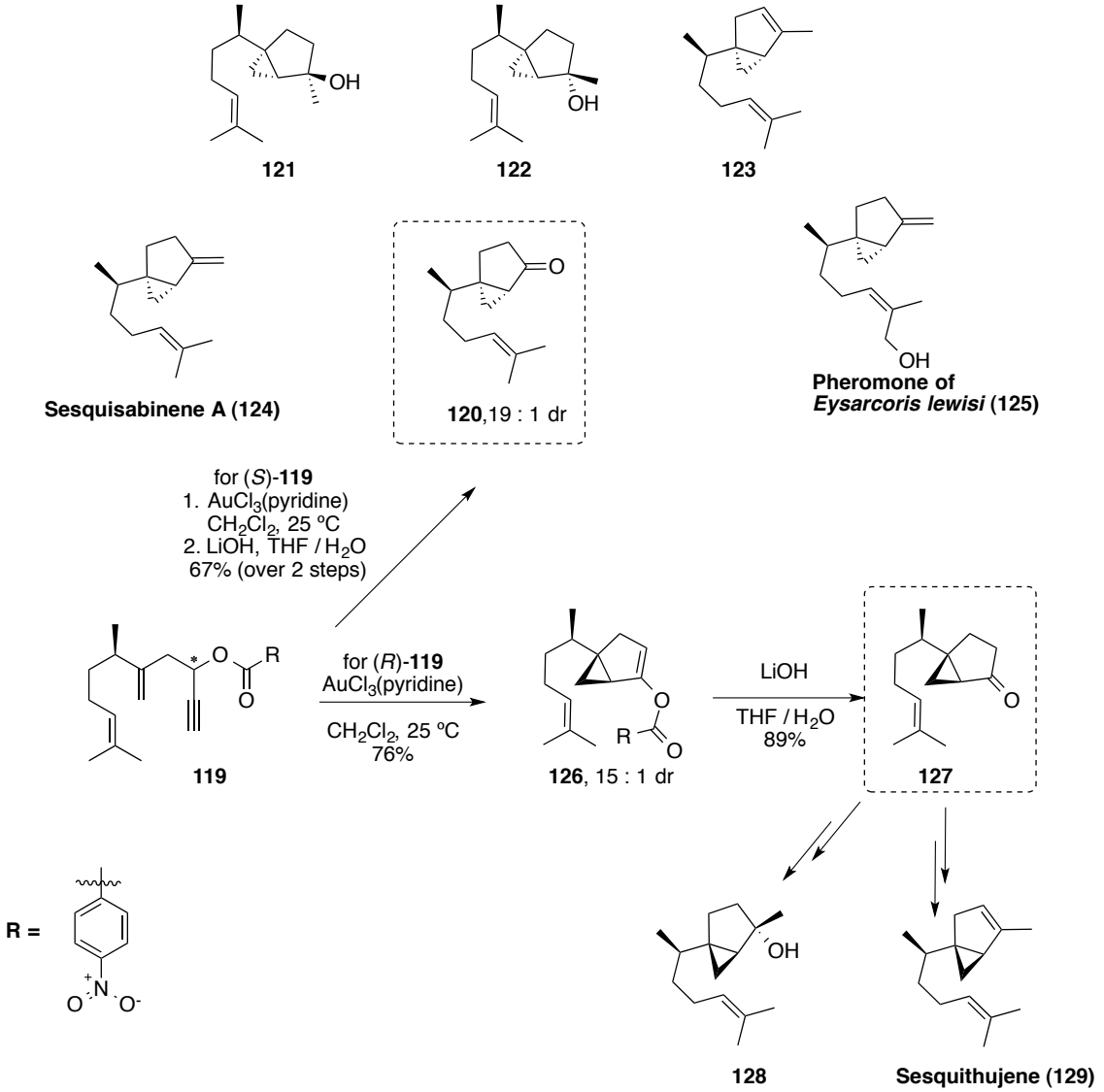
4. Reactions of propargyl carboxylates

4.1 1,2-Carboxylate shift of propargyl esters

The Ohloff-type reaction of propargyl carboxylates promoted by carbophilic π-acid catalysts is considered a safe alternative to the intramolecular cyclopropanation of α-diazoketones. The total synthesis of sesquisabinene A **124**, sesquithujene **129** and various terpenoids of these families as well as the formal synthesis of cedrene and cedril, which were accomplished by Fürstner and Schlecker are good exemplifications of the application of this concept towards an increasing molecular complexity (Scheme 28). [71] The chirality transfer of the enyne propargylic center into the

(70) Bellavance, G.; Barriault, L. *Angew. Chem. Int. Ed.* **2014**, *53*, 6701−6704.
(71) Fürstner, A.; Schlecker, A. *Chem. Eur. J.* **2008**, *14*, 9181–9191.

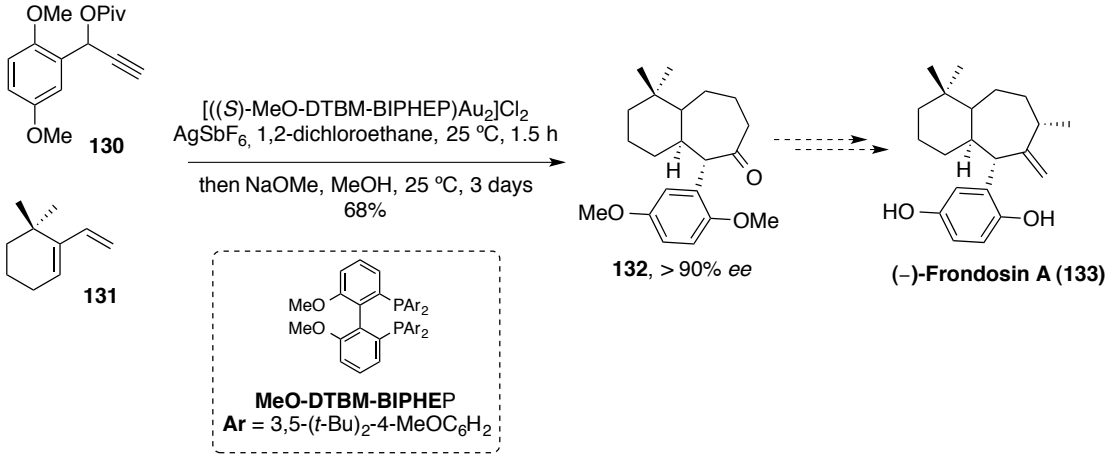
bicyclo[3.1.0]ketone stereostructure could be achieved by gold-catalyzed cycloisomerization. The highly diastereoselective gold(III)-catalyzed rearrangement of the (*S*)-**119** diastereomer followed by the hydrolysis of the initially formed vinyl ester furnished bicycle **120**, the precursor for sesquisabinene **124**. In the same way, the (*R*)-**119** diastereomer was cycloisomerized to provide cyclopentanone **127** after saponification. The bicyclo[3.1.0]ketone intermediates **120** and **127** were further converted into natural products and a host of sesquisabina and sesquithuja derivatives.



Scheme 28. Total syntheses of sesquisabinene and sesquithujene terpenoid families.

A similar noble metal-catalyzed rearrangement of propargyl acetates was used as a key step in the total syntheses of (−)-α-cubebene, (−)-cubebol, sesquicarene and related

terpenes.[72,73] The expansion of this concept was illustrated in the synthesis of the frondosins A and B scaffold (Scheme 29).[74] The mixture of propargyl pivaloate **130** and cyclohexene **131** was exposed to (*S*)-OMe-DTBM-BIPHEP-gold(I) complex leading to the formation of the corresponding bicyclic cycloheptenyl pivaloate *via* intramolecular cyclopropanation followed by a formal homo-Cope rearrangement. The *in situ* hydrolysis of the vinyl ester followed by an epimerization under basic conditions provided the thermodynamically more favored ketone **132** and completed the formal synthesis of frondosins A and B.

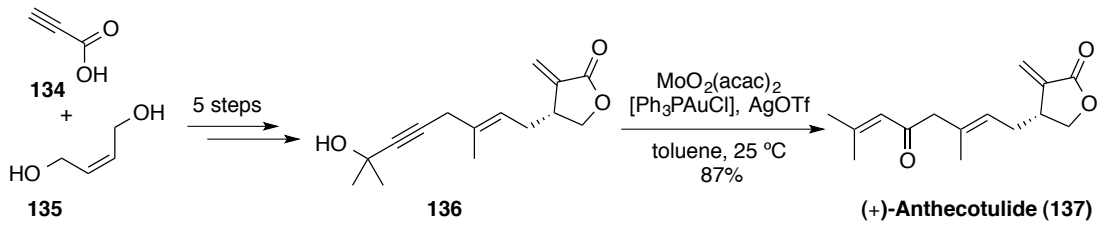


Scheme 29. Approach to the scaffold of frondosins A and B.

4.2 Meyer-Schuster rearrangement

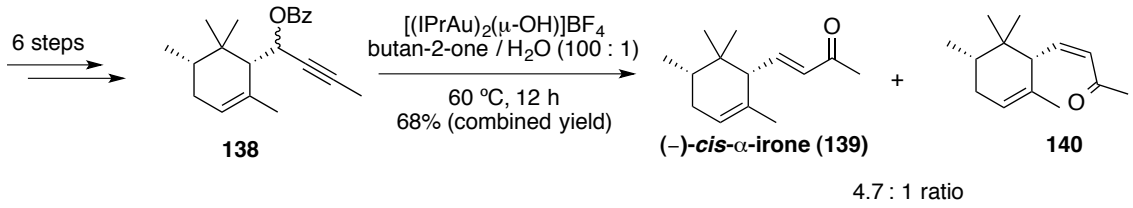
The gold-mediated Meyer-Schuster rearrangement is a mild method to convert propargylic alcohols into α,β-unsaturated ketones. The efficiency of this synthetic tool was nicely demonstrated in the total synthesis of the biologically active sesquiterpene lactone (+)-anthecotulide **137** (Scheme 30).[75] The treatment of propargylic alcohol **136** with a combination of MoO_2(acac) and a gold(I) complex provided the desired (+)-anthecotulide **137** in high yield. Remarkably, no isomerization of the trisubstituted olefin into conjugation with the ketone was observed.

(72) Fürstner, A.; Hannen, P. *Chem. Eur. J.* **2006**, *12*, 3006–3019.
(73) Fehr, C.; Galindo, J. *Angew. Chem. Int. Ed*. **2006**, *45*, 2901−2904.
(74) Garayalde, D.; Krüger, K.; Nevado, C. *Angew. Chem. Int. Ed.* **2011**, *50*, 911–915.
(75) Hodgson, D. M.; Talbot, E. P. A.; Clark, B. P. *Org. Lett.* **2011**, *13*, 5751–5753.



Scheme 30. Total synthesis (+)-anthecotulide.

The application of this strategy was also illustrated in the synthesis of bimatoprost and latanoprost[76] and in the synthesis of racemic α-ionone.[77] The potential utility of the gold(I)-catalyzed Meyer-Schuster rearrangement for the formation of α,β-unsaturated ketones in the context of target-oriented synthesis was exemplified in the synthesis of (−)-*cis*-α-irone **139**, a perfume ingredient (Scheme 31).[78] Exposing benzoate **138** to dinuclear NHC gold(I) catalyst resulted in the formation of a separable (*E*)-(−)-α-irone **139** and (*Z*)-(−)-α-irone **140** mixture in 68% combined yield. The (*Z*)-isomer **140** was converted into the desired (−)-*cis*-α-irone in nearly quantitative yield by iodine induced *Z*→*E* isomerization.



Scheme 31. Total synthesisof (−)-*cis*-α-irone.

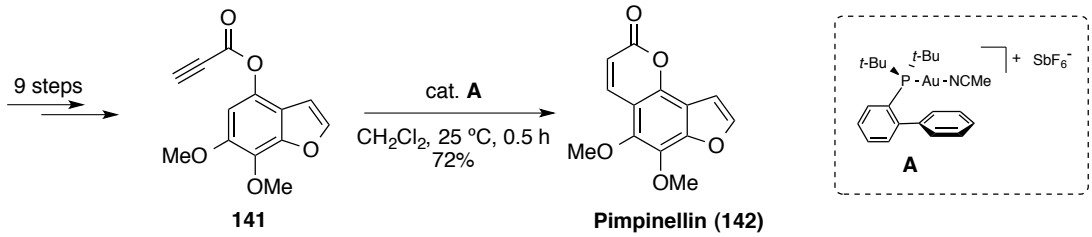
5. Hydroarylation

5.1 Hydroarylation of alkynes

The advantages of gold catalysis for the generation of functionalized polycyclic systems have been exemplified in the total synthesis of the coumarine-containing natural products pimpinellin **142**, fraxetin, and purpurasol (Scheme 32).[79] The desired alkyne **141**, precursor for the cyclization, was prepared in a linear sequence from vanillin in 9 steps. The late stage intramolecular hydroarylation of the aryl propiolate **141** proceeded

(76) Zanoni, G.; D'Alfonso, A.; Porta, A.; Feliciani, L.; Nolan, S. P.; Vidari, G. *Tetrahedron* **2010**, *66*, 7472−7478.
(77) Merlini, V.; Gaillard, S.; Porta, A.; Zanoni, G.; Vidari, G.; Nolan, S. P. *Tetrahedron Lett.* **2011**, *52*, 1124−1127.
(78) Bugoni, S.; Boccato, D.; Porta, A.; Zanoni, G.; Vidari, G. *Chem. Eur. J.* **2015**, *21*, 791–799.
(79) Cervi, A.; Aillard, P.; Hazeri, N.; Petit, L.; Chai, C. L. L.; Willis, A. C.; Banwell, M. G. *J. Org. Chem*. **2013**, *78*, 9876−9882.

smoothly under mild conditions in the presence of cationic JohnPhos gold(I) complex and furnished the natural product pimpinellin **142** in a good yield. The same approach was used for the synthesis of fraxetin and purpurasol.

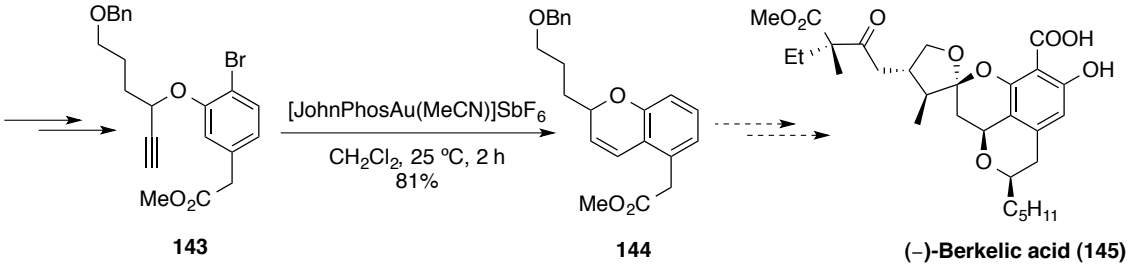


Scheme 32. Total synthesis of pimpinellin.

The same group also accomplished the synthesis of furanosesquiterpenes crassifolone and dihydrocrassifolone *via* intramolecular gold-catalyzed Michael addition of a furan moiety to an alkyne.[80] The total synthesis of natural alkaloid (−)-cryptopleurine was achieved by *6-endo-dig* cyclization of an arylalkyne to form the phenanthrene ring system.[81] A *7-exo-dig* alkyne hydroarylation proved to be a powerful tool for the efficient access to dibenzocycloheptanoids, which was illustrated by the synthesis of reticuol.[82] The benefits of a gold-catalyzed hydroarylation / cyclization cascade for the assembly of complex indoline skeletons of natural products have been nicely illustrated by the work of Wang *et al.* and the application of this methodology in the formal synthesis of the akuammiline alkaloid minfiensine.[83]

The utility of the gold catalyzed hydroarylation were nicely illustrated by the synthesis of tetracyclic core of berkelic acid (Scheme 33).[84] The cyclization of aryl propargyl ether **143** mediated by a cationic gold(I) complex efficiently provided the chromene fragment **144.** In contrast, $PtCl_4$ delivered the desired product in poor yield.

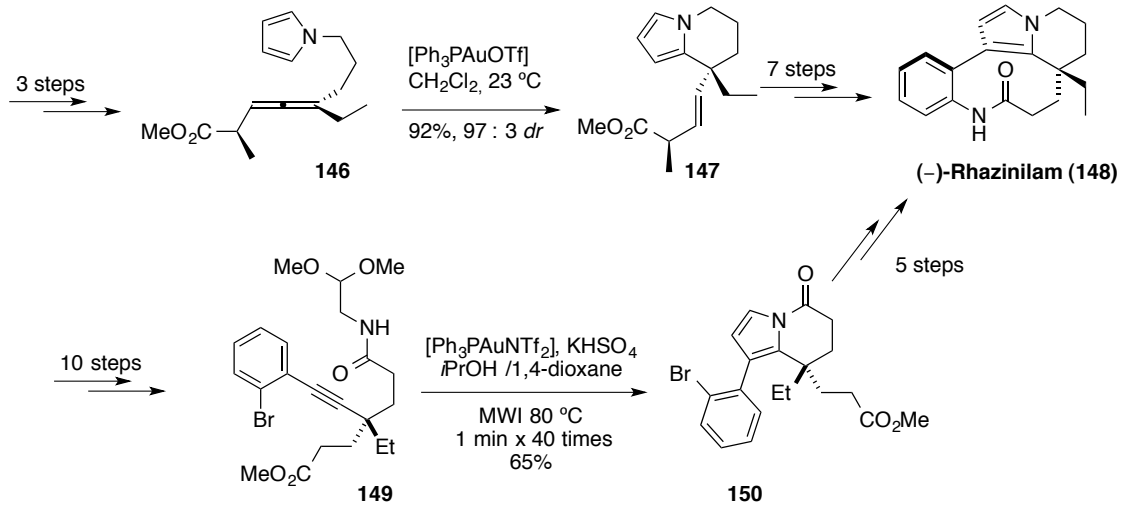
(80) Menon, R. S; Banwell, M. G. *Org. Biomol. Chem.* **2010**, *8*, 5483–5485.
(81) Stoye, A.; Opatz, T. *Eur. J. Org. Chem*. **2015**, 2149−2156.
(82) Pflästerer, D.; Rettenmeier, E.; Schneider, S.; de Las Heras Ruiz, E.; Rudolph, M.; Hashmi, A. S. K. *Chem. Eur. J.* **2014**, *20*, 6752−6755.
(83) Liu, Y.; Xu, W.; Wang, X. *Org. Lett.* **2010**, *12*, 1448−1451.
(84) Brimble, M. A.; Haym, I.; Sperry, J.; Furkert, D. P. *Org. Lett.* **2012**, *14*, 5820–5823.



Scheme 33. The synthesis of berkelic acid's tetracyclic core.

5.2 Hydroarylation of allenes

The allene hydroarylation promoted by π-acid catalysts, such as gold salts and complexes, is a powerful tool for the generation of complex architectures of natural products. The enantioselective total synthesis of (−)-rhazinilam **148** was accomplished by gold(I)-catalyzed hydroarylation of allene **146** (Scheme 34).[85] The intramolecular pyrrole addition to the gold-activated allene generated indolizine **147** with nearly complete transfer of the allene chirality. The synthesis of (−)-rhazinilam was achieved from this intermediate in 7 additional steps. The alternative synthesis of (−)-rhazinilam was developed by Tokuyama *et al.* relying on a gold(I)-catalyzed cyclization cascade (Scheme 34).[86] Alkyne **149** was converted to the desired indolizinone **150** through the following sequence of transformations: an intramolecular hydroamination of alkyne occurring in a *6-exo-dig* fashion to generate an enamide, its cyclization with the terminal acetal moiety and further aromatization provided the desired product **150**.

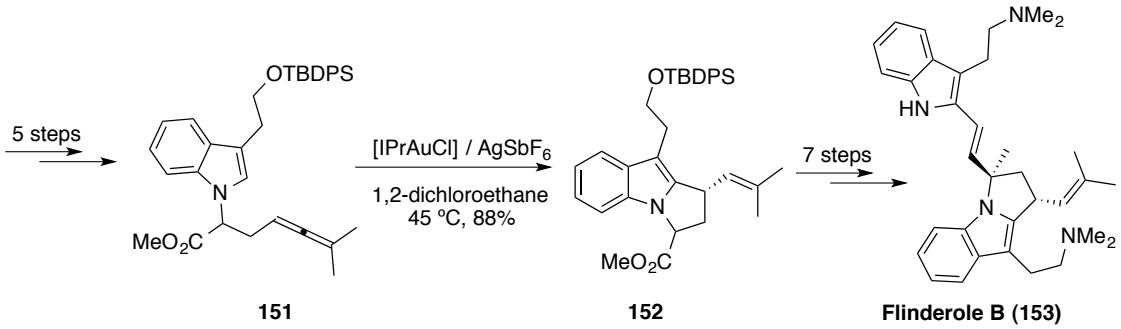


Scheme 34. Total synthesis of (−)-rhazinilam.

(85) Liu, Z.; Wasmuth, A. S.; Nelson, S. G. *J. Am. Chem. Soc.* **2006**, *128*, 10352–10353.
(86) Sugimoto, K.; Toyoshima, K.; Nonaka, S.; Kotaki, K.; Ueda, H.; Tokuyama, H. *Angew. Chem. Int. Ed.* **2013**, *52*, 7168–7171.

General Introduction. Gold In Total Synthesis.

The potential utility of the gold(I)-catalyzed allene hydroarylation was illustrated by the group of Toste in their total synthesis of flinderole B and C (Scheme 35).[87] Pyrrolidine **152** was obtained from allenylindole **151** by exposure of allene **151** to an *in situ* generated cationic gold complex at slightly elevated temperature. Further elaboration of tricycle **152** completed the synthesis of bisindole alkaloids flinderole B and C.



151 **152** **Flinderole B (153)**

Scheme 35. Total synthesis of flinderole B.

6. Oxidation reactions

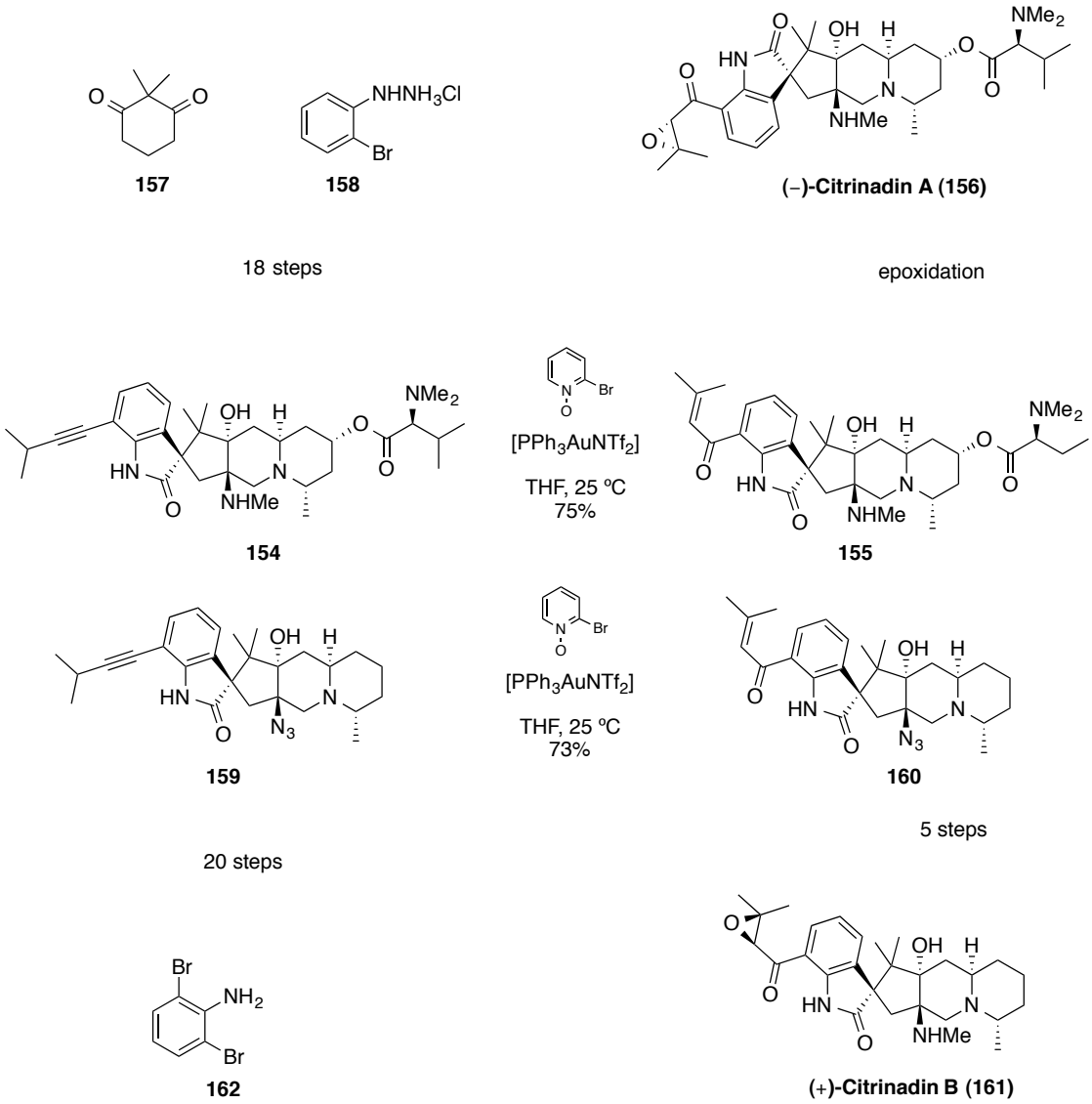
In 2007 it was discovered that *N*-oxides as well as sulfoxides could effect the oxygen transfer to alkynes in the presence of gold.[88] Since then a number of reports where this transformation was employed as a key step in target-oriented synthesis have been disclosed. Zhang's group accomplished the highly diastereoselective synthesis of (±)-cermizine from the corresponding tertiary aliphatic amine[89] using a two-step procedure for the piperidin-4-one formation. This synthesis consists of an *m*-CPBA mediated oxidation of amine to *N*-oxide, a gold(I)-catalyzed intramolecular oxidation of the alkyne to generate an α-oxo-gold carbene followed by a formal C−H insertion. The same group applied this methodology to the synthesis of (+)-lentiginosine[90] one year later. The advantages of the two-step piperidin-4-one formation were demonstrated in the total synthesis of the 12-membered macrolactone (±)-decinine by Yang and co-workers.[91] The generation of 2,5-disubstituted oxazole from alkynes and nitriles

(87) Zeldin, R. M.; Toste, F. D. *Chem. Sci.* **2011**, *2*, 1706–1709.
(88) (a) Li, G.; Zhang, L. *Angew. Chem. Int. Ed.* **2007**, *46*, 5156–5159. (b) Shapiro, N. D.; Toste, F. D. *J. Am. Chem. Soc.* **2007**, *129*, 4160–4161.
(89) Cui, L.; Peng, Y.; Zhang, L. *J. Am. Chem. Soc.* **2009**, *131*, 8394−8395.
(90) Cui, L.; Zhang, L. *Sci. China, Chem*. **2010**, *53*, 113−118.
(91) Shan, Z.-H.; Liu, J.; Xu, L.-M.; Tang, Y.-F.; Chen, J.-H.; Yang, Z. *Org. Lett.* **2012**, *14*, 3712–3715.

employing gold catalysis developed by Zhang *et al.* found an application in the synthesis of pimprinaphine.[92]

The gold(I)-mediated regioselective oxidation of alkynes to enones was applied in two independent reports: the total synthesis of (−)-citrinadin A **156** by Martin *et al.*[93] and the total synthesis of (+)-citrinadin B **161** by Wood *et al*. (Scheme 36).[94] The α,β-unsaturated carbonyl compound **155** and **160** were prepared from alkynes **154** and **159** respectively, using [$Ph_3PAuNTf_2$] in THF to trigger the gold(I)-catalyzed oxidation. The advanced intermediates **155** and **160** were converted respectively into (−)-citrinadin A **156** by subsequent epoxidation and (+)-citrinadin B **161** in 5 additional steps. These synthetic achievements led to the revision of the configuration of the citrinadins.

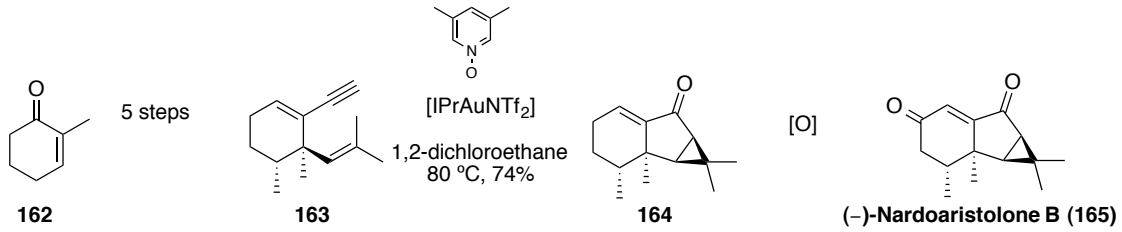
(92) He, W.; Li, C.; Zhang, L. *J. Am. Chem. Soc.* **2011**, *133*, 8482−8485.
(93) Bian, Z.; Marvin, C. C.; Martin, S. F. *J. Am. Chem. Soc.* **2013**, *135*, 10886–10889.
(94) Kong, K.; Enquist Jr, J. A.; McCallum, M. E.; Smith, G. M.; Matsumaru, T.; Menhaji-Klotz, E.; Wood, J. L. *J. Am. Chem. Soc.* **2013**, *135*, 10890–10893.



Scheme 36. Total syntheses of (−)-citrinadin A and (+)-citrinadin B.

The enantioselective total synthesis of (−)-nardoaristolone B **165** was achieved using a gold(I)-catalyzed oxidative cyclization of 1,5-enyne **163** (Scheme 37).[95] Careful optimization of the reaction conditions along with uncovering the optimal intermolecular oxidant favored the desired oxidative cyclization pathway over the cycloisomerization and led to the required tricyclic ketone **164**, isolated in 74% yield. The allylic Pd-catalyzed radical oxidation of enone **164** completed the 7-step synthesis of (−)-nardoaristolone B.

(95) Homs, A.; Muratore, M. E.; Echavarren, A. M. *Org. Lett.* **2015**, *17*, 461–463.



Scheme 37. Total synthesis of (−)-nardoaristolone B.

The gold-catalyzed tandem cycloisomerization / oxidation of homopropargyl amides for the synthesis of enantionenriched γ-lactams established by Ye *et al.* was used for the synthesis of (−)-bgugaine.[96] A similar gold(I)-catalyzed synthesis of optically active pyrrolidin-3-ones found an application in the synthesis of (−)-irniine.[97] An illustration of a gold-catalyzed intermolecular alkyne oxidation employed for the preparation of 3-coumaranones can be found in the synthesis of the natural product sulfuretin.[98] The synthetic utility of the gold(I)-mediated intermolecular oxidation of allyl homopropargyl esters with *N*-oxide was demonstrated by the formal synthesis of (±)-kumausallene accomplished by the group of Tae.[99]

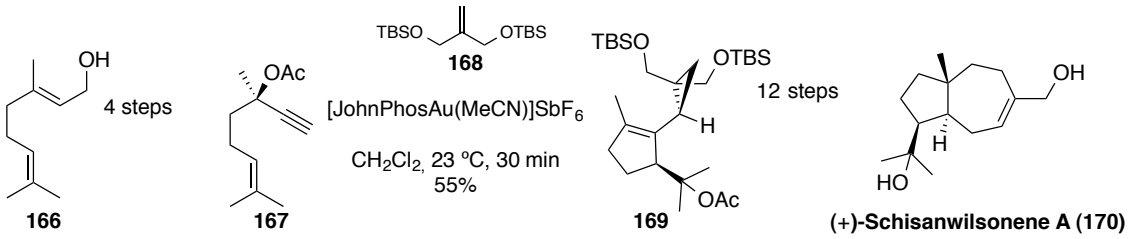
7. Tandem-cascade reactions

7.1 Tandem reactions via enyne cyclization

The ability of gold salts and complexes to promote complex multistep transformations and significantly increase molecular complexity was illustrated by the total synthesis of the carotane-type sesquiterpenoid (+)-schisanwilsonene A **170** (Scheme 38).[100] Cyclopentene **167** was efficiently generated from the easily accessible 1,6-enyne **167** taking advantage of the gold-catalyzed tandem reaction of enynes bearing a propargyl acetate moiety. This transformation involves a cycloisomerization of the 1,6-enyne triggered by a cationic gold(I) complex followed by the acetate 1,5-migration to generate an α,β-unsaturated gold carbene, which undergoes intermolecular cyclopropanation with alkene **168**. It is remarkable that the intramolecular olefin attack to the alkynyl gold complex occurred faster than the 1,2-acyl migration. The further

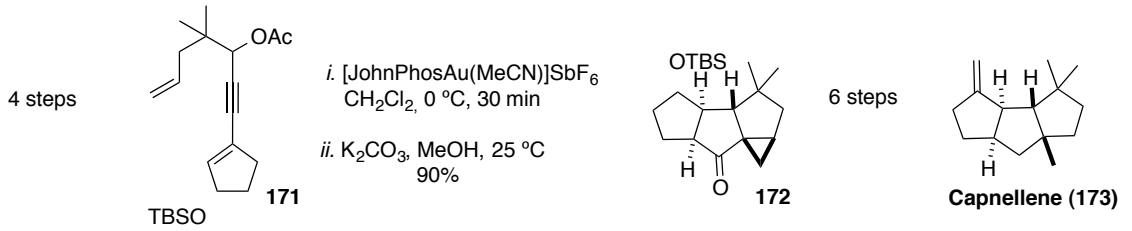
(96) Shu, C.; Liu, M.-Q.; Wang, S.-S.; Li, L.; Ye, L.-W. *J. Org. Chem*. **2013**, *78*, 3292−3299.
(97) Shu, C.; Li, L.; Yu, Y.-F.; Jiang, S.; Ye, L.-W. *Chem. Commun.* **2014**, *50*, 2522−2525.
(98) Shu, C.; Liu, R.; Liu, S.; Li, J.-Q.; Yu, Y.-F.; He, Q.; Lu, X.; Ye, L.-W. *Chem. Asian J.* **2015**, *10*, 91−95.
(99) Han, M.; Bae, J.; Choi, J.; Tae, J. *Synlett* **2013**, *24*, 2077−2080.
(100) Gaydou, M.; Miller, R. E.; Delpont, N.; Ceccon, J.; Echavarren, A. M. *Angew. Chem. Int. Ed.* **2013**, *52*, 6396–6399.

elaboration of the cyclopropyl intermediate **169** completed the synthesis of (+)-schisanwilsonene A.



Scheme 38. Total synthesis of (+)-schisanwilsonene A.

The application of a gold(I)-catalyzed cascade transformation was nicely demonstrated in the total synthesis of marine sesquiterpene capnellene **173** (Scheme 39).[101] In the presence of a cationic gold(I) complex, propargyl acetate **171** underwent a sequential acetate 1,3-migration to form an allenyl acetate followed by a Nazarov-type electrocyclization and finally an intramolecular cyclopropanation. Tetracyclic ketone **172** was obtained after *in situ* hydrolysis of the initially formed vinyl acetate. Capnellene was prepared in 6 steps from triquinane intermediate **172**.



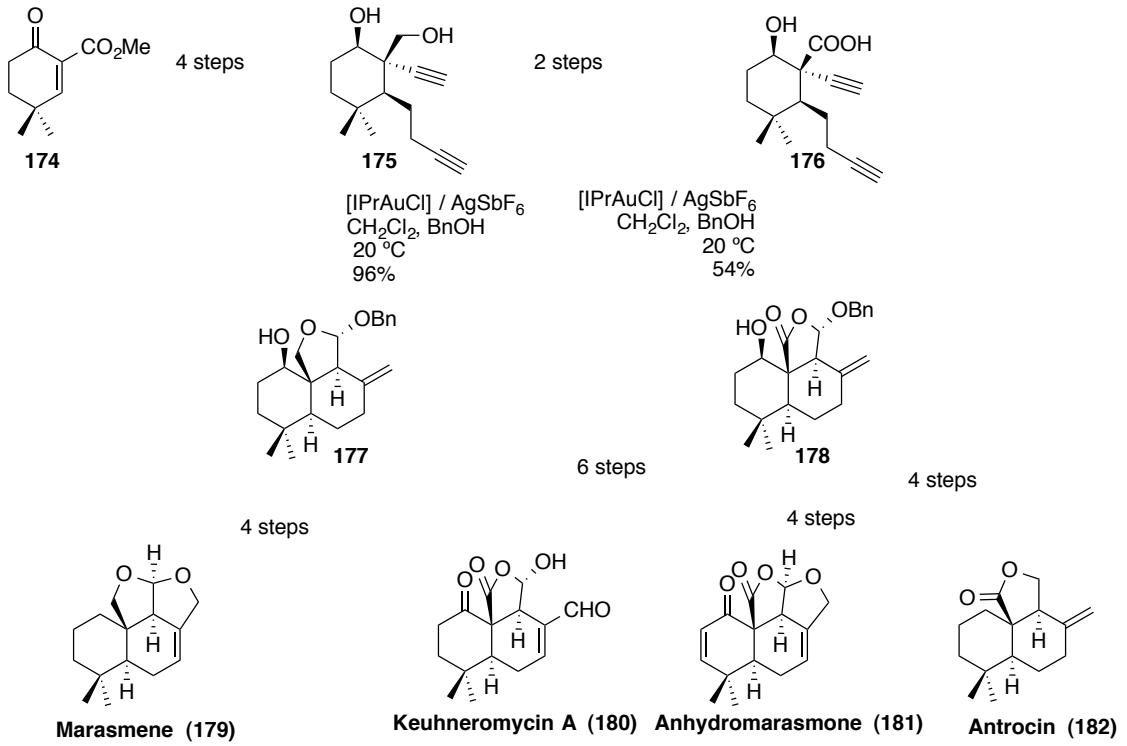
Scheme 39. Total synthesis of capnellene.

7.2 Diyne tandem reactions

The gold-catalyzed tandem reaction of 1,7-diynes found an application in the total synthesis of drimane-type sesquiterpenoids accomplished by Yang and co-workers (Scheme 40).[102] Extensive condition optimization on the closely related model showed that IPrAuCl / $AgSbF_6$ provided a high yield of the desired cascade product. The aforementioned catalyst proved to be equally efficient in the case of 1,7-diynes **175** and **176,** affording tricycles **177** and **178** respectively in good to excellent yields. This cascade transformation includes the intramolecular addition of the primary alcohol in a

(101) Lemière, G.; Gandon, V.; Cariou, K.; Hours, A.; Fukuyama, T.; Dhimane, A.-L.; Fensterbank, L.; Malacria, M. *J. Am. Chem. Soc.* **2009**, *131*, 2993–3006.
(102) Shi, H.; Fang, L.; Tan, C.; Shi, L.; Zhang, W.; Li, C.; Luo, T.; Yang, Z. *J. Am. Chem. Soc.* **2011**, *133*, 14944–14947.

5-endo-dig fashion to generate the furanone intermediate whose polarized olefin functionality acts as a nucleophile towards the other activated alkyne in a following *6-exo-dig* cyclization. The termination of the cascade by an external nucleophile leads to the tricyclic skeleton of the natural products. The straightforward functional group modification of the tricyclic intermediates completed the synthesis of 4 sesquiterpenoids. A similar gold-catalyzed tandem reaction of 1,7 diynes enabled the synthesis of cladiellins.[103]

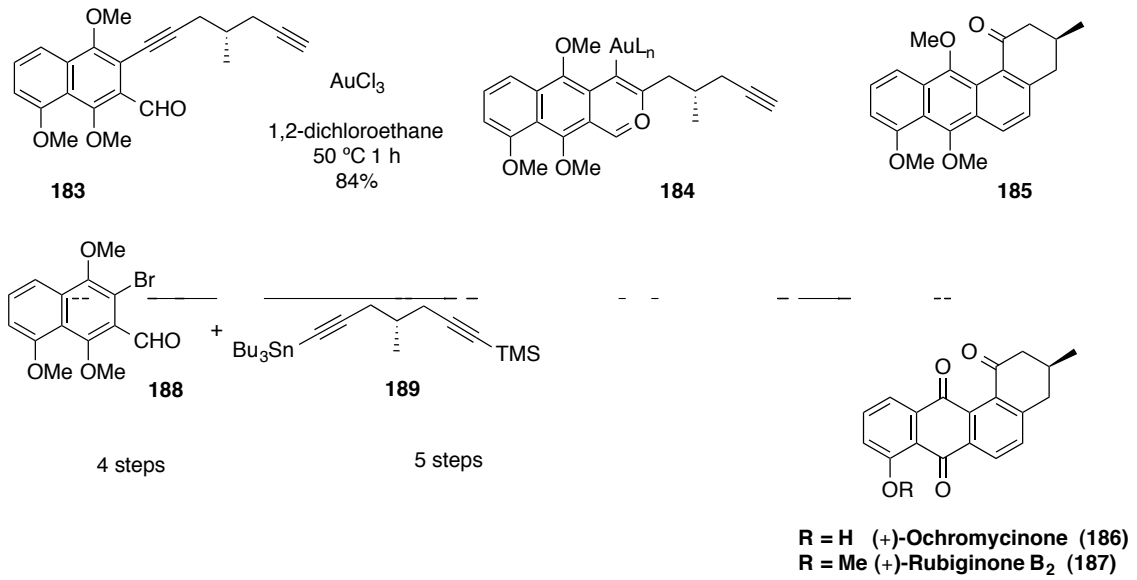


Scheme 40. Total synthesis of drimane-type sesquiterpenoids.

The gold-catalyzed cycloisomerization of *ortho*-alkynylbenzaldehydes is a practically useful method for the construction of highly functionalized carbocyclic ring systems. The total synthesis of (+)-ochromycinone **186** and (+)-rubiginone **187** was accomplished by Yamamoto and co-workers taking advantage of this gold-catalyzed intramolecular [4+2] benzannulation of tethered alkynes (Scheme 41).[104] The exposure of diyne **183** to $AuCl_3$ generated isobenzopyrylium cation **184** which underwent an intramolecular hetero-Diels-Alder reaction to give dihydrotetraphenone derivative **185**. Series of straightforward modifications provided angucyclinone antibiotics (+)-ochromycinone **186** and (+)-rubiginone B_2 **187**. The total synthesis of

(103) Yue, G.; Zhang,Y.; Fang, L.; Li, C.; Luo, T.; Yang, Z. *Angew. Chem. Int. Ed.* **2014**, *53*, 1837–1840.
(104) Sato, K.; Asao, N.; Yamamoto, Y. *J. Org. Chem.* **2005**, *70*, 8977−8981.

heliophenanthrone also highlights the utility of this transition metal-catalyzed domino process in the context of polycyclic system formation.[105]



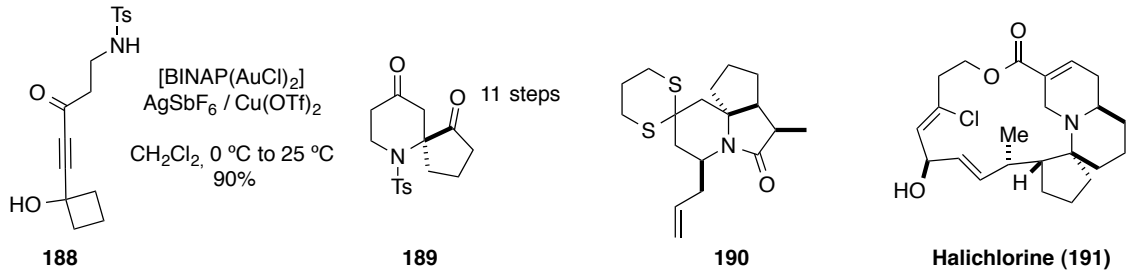
Scheme 41. Total synthesis of (+)-ochromycinone **186** and (+)-rubiginone B_2 **187**.

7.3 Alkyne tandem reactions

An efficient method of 6-azaspiro[4.5]decane skeleton construction was applied to the formal synthesis of (±)-halichlorine by Zhang and co-workers (Scheme 42).[106] A dual gold(I) / copper(II)-cocatalyzed tandem cyclization / semipinacol rearrangement of alkynyl cyclobutyl alcohol **188** proceeded *via* hydroamination of the gold the activated alkyne, in a *6-endo-dig* fashion, to generate a cyclic enamine which then underwent a Lewis acid-promoted semipinacol rearrangement. The gold(I) / copper(II) catalytic system proved to be optimal to trigger this transformation, whereas gold(I) complexes or copper(II) triflate alone showed low yield or no reactivity, respectively. The azaspirocycle **189** was further converted to previously synthesized intermediate **190**, completing the formal synthesis of (±)-halichlorine in 11 steps.

(105) Dyker, G.; Hildebrandt, D. *J. Org. Chem.* **2005**, *70*, 6093−6096.
(106) Zhu, D.-Y.; Zhang, Z.; Mou, X.-Q.; Tu, Y.-Q.; Zhang, F.-M.; Peng, J.-B.; Wang, S.-H.; Zhang, S.-Y. *Adv. Synth. Catal.* **2015**, *357*, 747−752.

General Introduction. Gold In Total Synthesis.



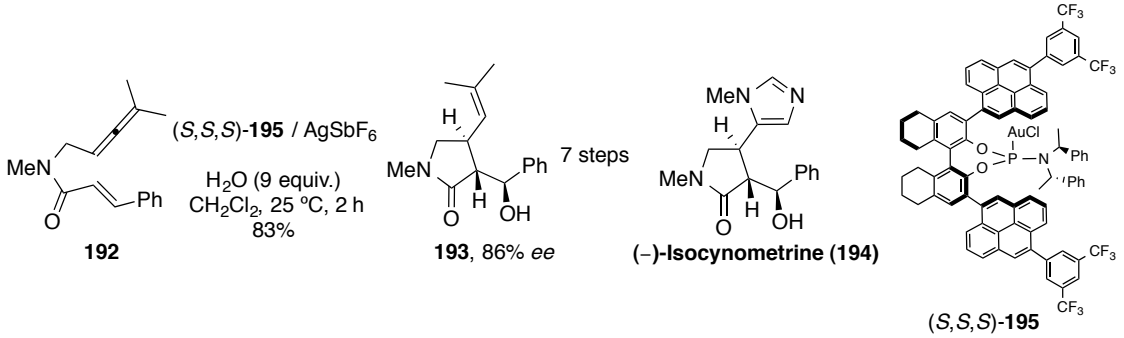
188 **189** **190** **Halichlorine (191)**

Scheme 42. Formal synthesis of (±)-halichlorine.

Rapid syntheses of (±)-pterocarpans, isoflavones and their analogues was accomplished by Skouta and Li employing a gold(I)-catalyzed annulation of hydroxyarylalhedydes and alkynes.[107] Another interesting example of gold(I)-mediated domino reaction of homopropargylic alkoxyalkylamines is presented in the formal synthesis of (−)-pseudodistomin B developed by Rhee and co-workers.[108]

7.4 Cycloaddition-alkoxylation of allenes

The methodology for the enantioselective synthesis of 3,4-disubstituted pyrrolidines developed by Toste *et al.* was successfully applied to the formal synthesis of (−)-isocynometrine **194** (Scheme 43).[109] The substituted allene **192** was converted in the presence of water to the corresponding γ-lactam **193** in 86% *ee* employing the bulky chiral phosphoramidite gold(I) catalyst **195**. Elaboration of lactam **193** resulted in a previously synthesized intermediate and completed the formal synthesis of (−)-isocynometrine.



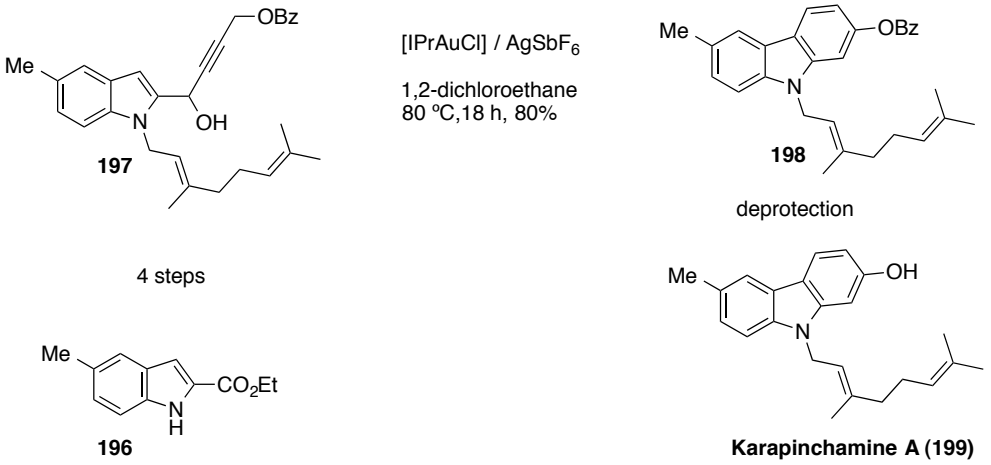
192 **193**, 86% *ee* **(−)-Isocynometrine (194)** (*S*,*S*,*S*)-**195**

Scheme 43. Formal synthesis of (−)-isocynometrine.

(107) Skouta, R.; Li, C.-J. *Tetrahedron Lett.* **2007**, *48*, 8343−8346.
(108) Lee, J. H.; Jeong, W.; Rhee, Y. H. *Synthesis* **2014**, *46*, 2155−2160.
(109) González, A. Z.; Benitez, D.; Tkatchouk, E.; Goddard, III, W. A.; Toste, F. D. *J. Am. Chem. Soc.* **2011**, *133*, 5500−5507.

8. Synthesis of (hetero)arenes

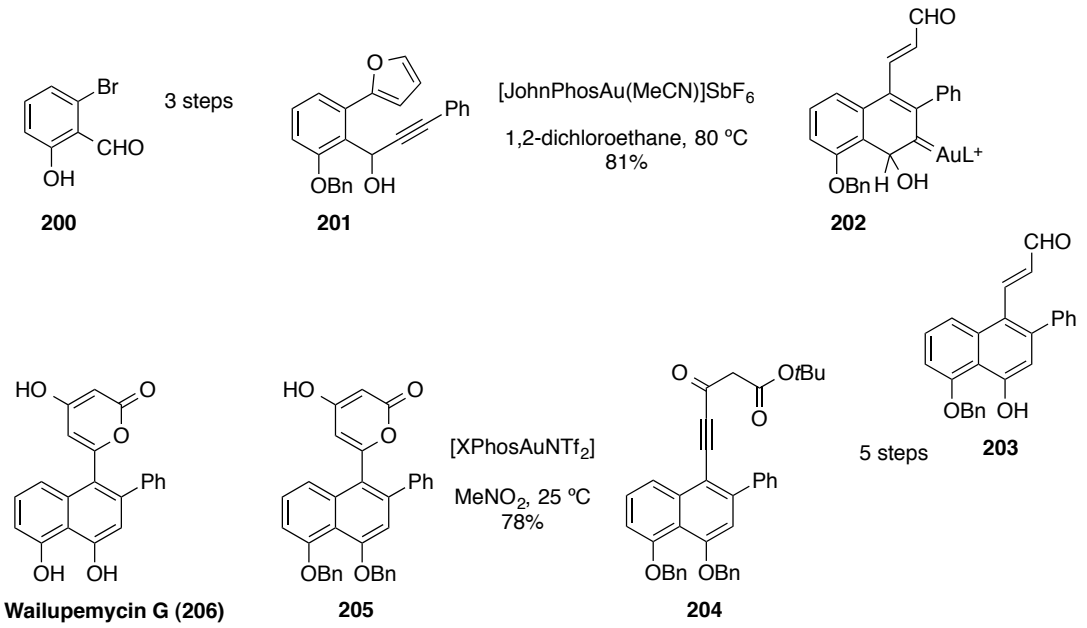
An efficient method of carbazole formation from indolyl alkynols employing gold(I) catalysis was developed by the group of Ma and applied to the synthesis of karapinchamine A **199** (Scheme 44).[110] The exposure of alkyne **197,** easily accessible from indole **196,** to [IPrAuCl] / $AgSbF_6$ at 80 ºC led to the formation of the desired carbazole **198** in 80% yield. Ma *et al.* proposed that this gold(I)-promoted cascade transformation consists of a sequential 1,3-shift of the carboxylate to form an allenyl benzoate, the hydroarylation of the allene by indole followed by elimination of water and a 1,2-hydride shift.



Scheme 44. Total synthesis of karapinchamine A.

The advantages of the gold(I)-mediated arene formation was clearly illustrated in the synthesis of wailupemycin G **206** (Scheme 45).[111] The gold(I)-catalyzed intramolecular hydroarylation of alkyne **201** by furan followed by 1,2-hydride shift and protodeauration led to 1-naphthol **203**. The functional group modification of aldehyde **203** resulted in the synthesis of ketoester **204**, setting the stage for a gold(I)-catalyzed alkyne hydrocarboxylation. The desired pyrone **205** was obtained in 78% yield using [XPhosAuNTf$_2$], its subsequent debenzylation furnished wailupemycin G.

(110) Qui, Y.; Zhou, J.; Fu, C.; Ma, S. *Chem. Eur. J.* **2014**, *20*, 14589−14593.
(111) Chen, Y.; Wang, L.; Sun, N.; Xie, X.; Zhou, X.; Chen, H.; Li, Y.; Liu, Y. *Chem. Eur. J.* **2014**, *20*, 12015−12019.



Scheme 45. Total synthesis of wailupmycin G.

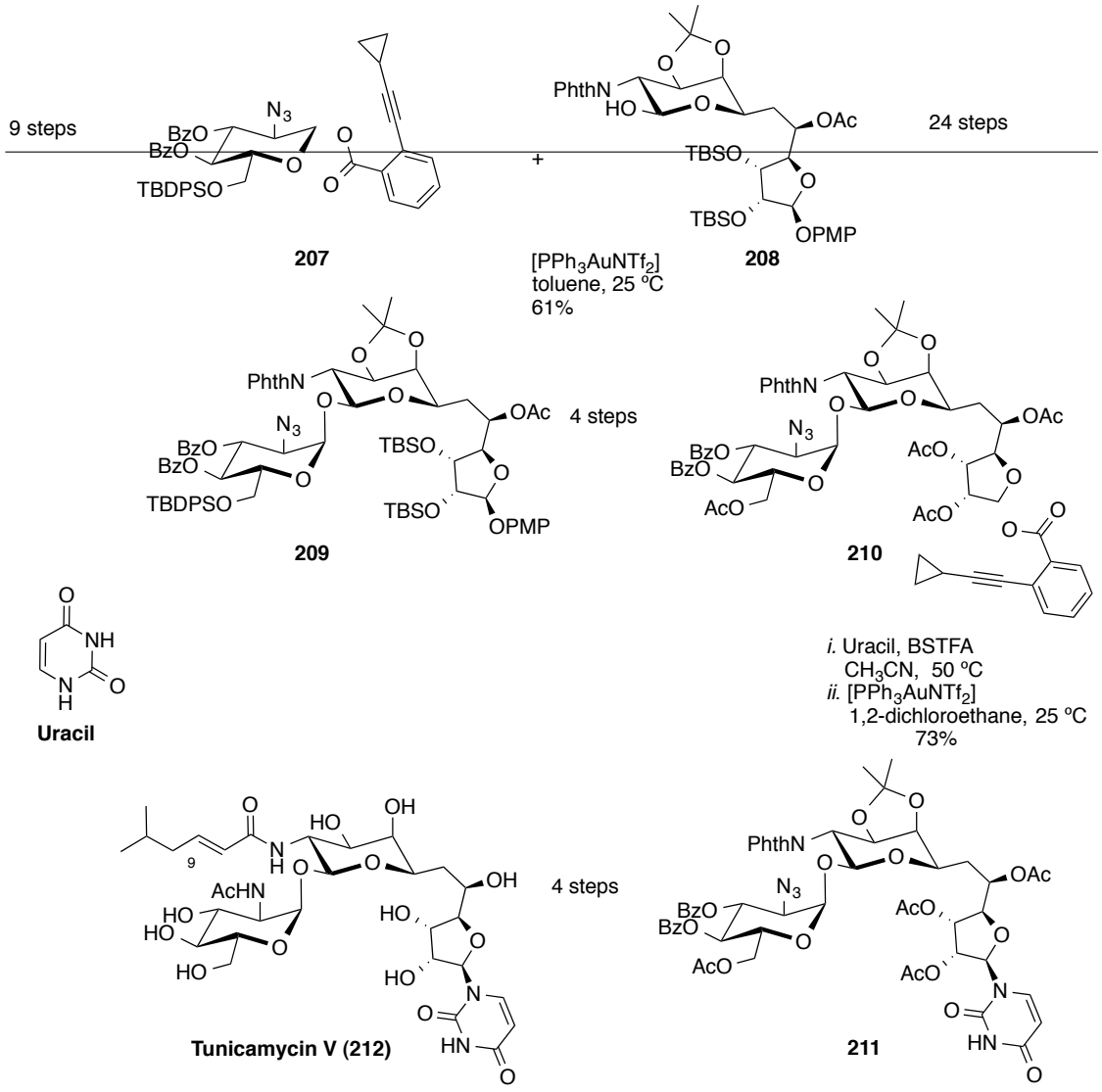
A sensitive furan moiety was formed from an alkynyl diol using gold catalysis in the total synthesis of (±)-cafestol.[112] Interestingly, it was work it was found that the presence of silver salts were detrimental for the reaction since they caused unwanted side transormations. Premixing [PPh_3AuCl] and $AgBF_4$ followed by filtration was required to prevent byproducts formation. The gold-mediated synthesis of phenols from furans was also applied to the preparation of jungianol and *epi*-jungianol.[113]

9. Glycosylation

In 2011, Yu and co-workers established an efficient methodology for the *N*-glycosylation of pyrimidines and purines with glycosyl *ortho*-alkynyl benzoates.[114] The same year, the extension of this method to the *O*-glycosylation of alcohols was applied to the synthesis of ginsenoside Rh2, chikusetsusaponin-LT8 [115] and lupane-type saponins.[116] The total synthesis of tunicamycin V **212** is a good demonstration of the benefits of the gold(I)-catalyzed *N*- and *O*-glycosylation for the preparation of complex nucleosides (Scheme 46).[117] The *O*-glycosylation of lactol **207** by *ortho*-alkynyl benzoate **208** was achieved by employing [PPh_3AuNTf_2], providing the desired β,α-

(112) Zhu, L.; Luo, J.; Hong, R. *Org. Lett.* **2014**, *16*, 2162−2165.
(113) Hashmi, A. S. K.; Ding, L.; Bats, J. W.; Fischer, P.; Frey, W. *Chem. Eur. J.* **2003**, *9*, 4339−4345.
(114) Zhang, Q.; Sun, J.; Zhu, Y.; Zhang, F.; Yu, B. *Angew. Chem. Int. Ed.* **2011**, *50*, 4933−4936.
(115) Liao, J.; Sun, J.; Niu, Y.; Yu, B. *Tetrahedron Lett.* **2011**, *52*, 3075−3078.
(116) Li, Y.; Sun, J.; Yu, B. *Org. Lett.* **2011**, *13*, 5508−5511.
(117) Li, J.; Yu, B. *Angew. Chem. Int. Ed.* **2015**, *54*, 6618−6621.

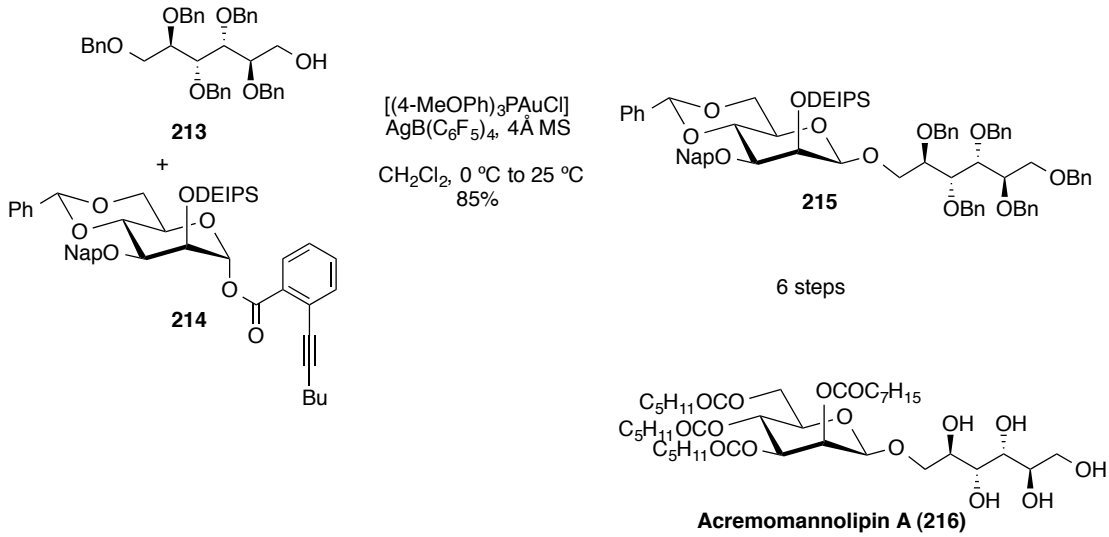
trehalose **209** which was converted into *ortho*-alkynyl benzoate **210**, required for the second glycosylation event. The *N*-glycosylation of uracil with *ortho*-alkynyl benzoate **210** was accomplished under slightly modified conditions to give the advanced intermediate **211** that was converted into tunicamycin V.



Scheme 46. Total synthesis of tunicamycin V.

The β-mannosylation with *ortho*-alkynyl benzoates was applied to the total synthesis of acremomannolipin A **216** (Scheme 47).[118] The desired β-mannoside **215** was obtained exclusively by exposing the mixture of *ortho*-alkynyl benzoate **214** and mannitol derived acceptor **213** to [(4-MeOPh)$_3$PAuCl] / AgB(C_6F_5)$_4$. Further elaboration of intermediate **215** provided acremomannolipin A as well as a library of analogues.

(118) Sun, P.; Wang, P.; Zhang, Y.; Zhang, X.; Wang, C.; Liu, S.; Lu, J.; Li, M. *J. Org. Chem.* **2015**, *80*, 4164–4175.



Scheme 47. Total synthesis of acremomannolipin A.

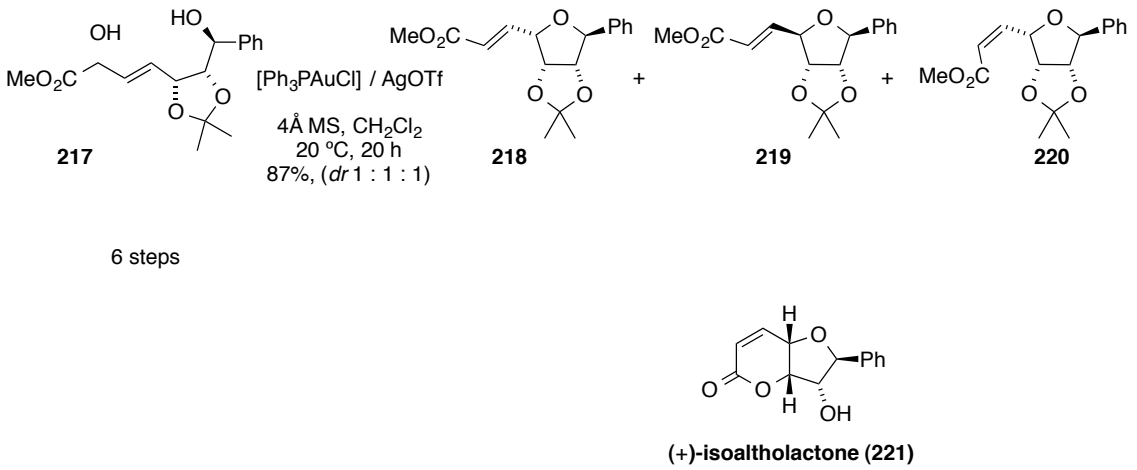
The *ortho*-alkynyl benzoate *O*-glycosylation has proven to be an essential tool in glycoside chemistry, which was brilliantly illustrated by the total synthesis of the pregnane hexasaccharide periploside A accomplished in 9.2% overall yield.[119] This impressive 76 step synthesis, with the longest linear sequence of 29 steps, relied on the gold(I)-catalyzed *O*-glycosylation of *ortho*-alkynyl benzoates to unite fragments of the hexasaccharide in the presence of labile moieties. The total synthesis of starfish saponin goniopectenoside B is another remarkable example of the utility of this transformation.[120]

10. Gold-catalyzed allylic substitution of free alcohols

Monoallylic diols are known to undergo cyclization in the presence of gold(I) to form tetrahydrofuranyl rings. This elegant transformation was applied as a key step in the total synthesis of (+)-isoaltholactone **221** (Scheme 48).[121] Treating acetonide **217** with [Ph_3PAuCl] / AgOTf in the presence of molecular sieves led to the formation of an *E*-/*Z*-mixtures of α,β-unsaturated esters **218**, **219** and **220**. Tetrahydrofurans **218**, **219** and **220** were separated and independently converted to (+)-isoaltholactone.

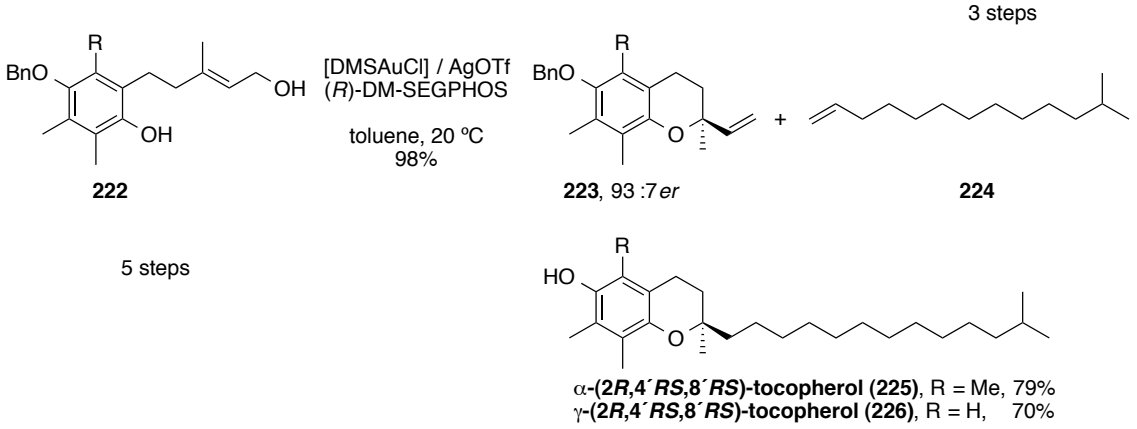
(119) Zhang, X.; Zhou, Y.; Zuo, J.; Yu, B. *Nat. Commun*. **2015**, *6*, 5879−5889.
(120) Xiao, G.; Yu, B. *Chem. Eur. J.* **2013**, *19*, 7708−7712.
(121) Unsworth, W. P.; Stevens, K.; Lamont, S. G.; Robertson, J. *Chem. Commun*. **2011**, *47*, 7659−7661.

General Introduction. Gold In Total Synthesis.



Scheme 48. Total synthesis of (+)-isoaltholactone.

A novel asymmetric gold(I)-catalyzed intramolecular allylic alkylation reaction was applied as a key step in the synthesis of the most biologically active members of the vitamin E family, α-tocopherol **225** and γ-tocopherol **226** (Scheme 49).[122] The chiral chromane fragment **223** was obtained in quantitative yield and 93 : 7 *er* by asymmetric allylic substitution of free alcohol **222** employing a chiral phosphine gold (I) complex. The cross metathesis of **233** and **224** followed by debenzylation furnished the natural products.



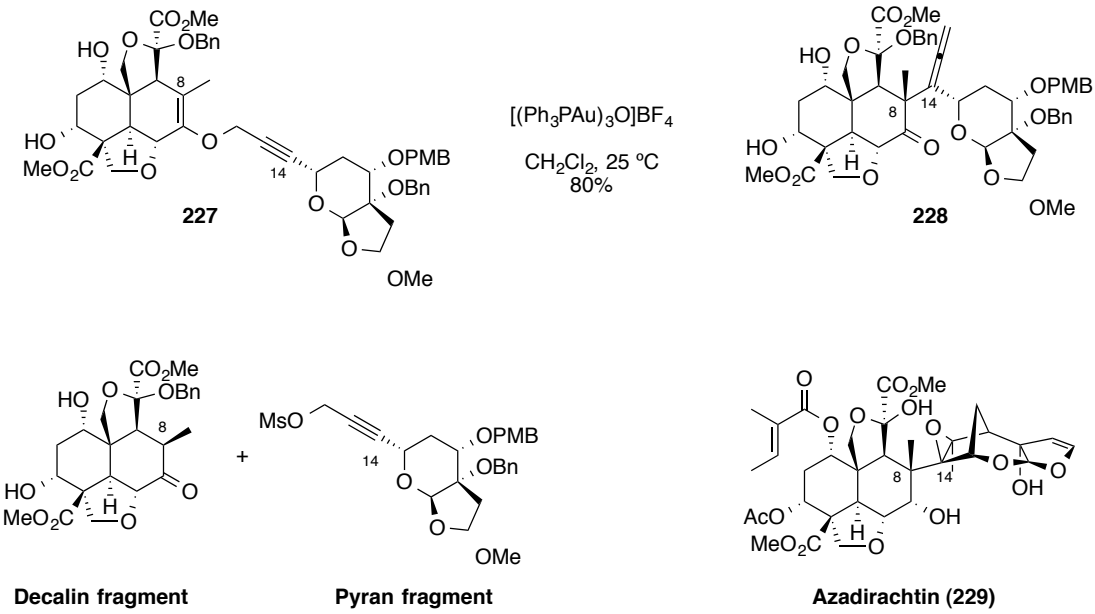
Scheme 49. Total synthesis of α-tocopherol and γ-tocopherol.

(122) Uria, U.; Vila, C.; Lin, M.-Y.; Rueping, M. *Chem. Eur. J.* **2014**, *20*, 13913−13917.

11. Other transformations catalyzed by gold

11.1 Gold-promoted Claisen rearrangement

A challenging example of a gold-mediated [3,3]-sigmatropic Saucy-Marbet rearrangement is presented in the total synthesis of azadirachtin **229** by Ley (Scheme 50).[123] The key C8−C14 bond was constructed by the gold(I)-catalyzed Claisen rearrangement of propargylic enol ether **227** which led to the formation of allene **228**. A similar efficiency of the [3,3]-sigmatropic rearrangement was observed when harsh thermal conditions were applied. Multistep functional group modification finally allowed to complete the remarkable total synthesis of azadirachtin.

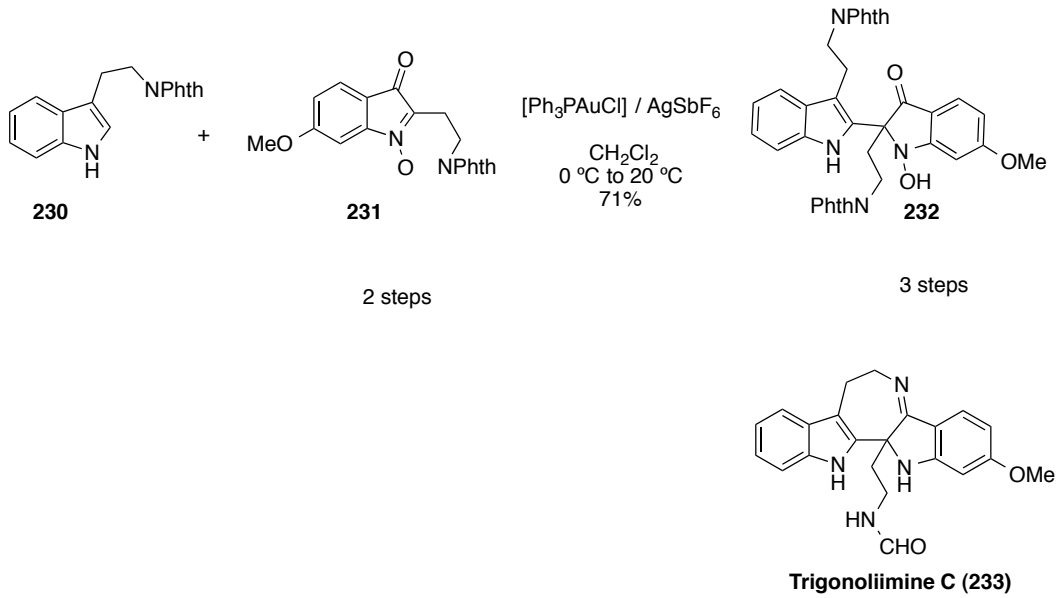


Scheme 50. Total synthesis of azadirachtin.

11.2 Gold-promoted indole C2 addition to isatogen

The total synthesis of the alkaloid (±)-trigonoliimine C was accomplished by employing an unusual gold(I)-catalyzed indole C2 addition to isatogen (Scheme 51).[124] Various tested Lewis acids ($InCl_3$, $Yb(OTf)_3$, $AgSbF_6$, AgOTf) resulted in the formation of complex mixtures, however the efficient addition at C2 of tryptamine derivative **230** to isatogen **231** was achieved using a phosphine gold(I) complex. The subsequent deprotection, condensation and formylation of **232** completed the synthesis of (±)-trigonoliimine C.

(123) Veitch, G. E.; Beckmann, E.; Burke, B. J.; Boyer, A.; Maslen, S. L.; Ley, S. V. *Angew. Chem. Int. Ed.* **2007**, *46*, 7629−7632.
(124) Reddy, B. N.; Ramana, C. V. *Chem. Commun.* **2013**, *49*, 9767−9769.



Scheme 51. Total synthesis of (±)-trigonoliimine C.

UNIVERSITAT ROVIRA I VIRGILI
TOTAL SYNTHESES OF NOVEL CANNABINOIDS AND LUNDURINES A¿C WITH A GOLDEN TOUCH
Mariia Kirillova

Chapter 1. Synthesis of (−)-Cannabimovone and Structural Reassignment of Anhydrocannabimovone

UNIVERSITAT ROVIRA I VIRGILI
TOTAL SYNTHESES OF NOVEL CANNABINOIDS AND LUNDURINES A¿C WITH A GOLDEN TOUCH
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Chapter 1. Synthesis of (−)-Cannabimovone and Structural Reassignment of Anhydrocannabimovone

Introduction

Cannabis sativa (Figure 1) has been used in natural medicine for centuries and still attracts significant interest owing to the biological and pharmaceutical activity of many of its metabolites.[1] More than 60 compounds, known as cannabinoids (group of C_{21} terpenophenolic compounds), are exclusively found in *Cannabis sativa*.[2] Due to the development of synthetic cannabinoids,[3,4] the unique components of *Cannabis sativa* are known as phytocannabinoids. The main members of this family are presented in Figure 2.

Figure 1. Photo *Cannabis sativa*

The most renowned compound is Δ^9-tetrahydrocannabinol (THC, **1**, Figure 2). Besides its well-known psychotropic effects, it shows interesting pharmacological activities as an analgesic, antiemetic, appetite stimulant and other activities.[5] Several total syntheses of **1**

(1) (a) Thakur, G. A.; Duclos Jr R. I.; Makriyannis, A. *Life Sci.* **2005**, *78*, 454−466. (b) *Marijuana and the Cannabinoids* (Ed. M. A. El'Sohly), Humana Press, **2007**. (c) Robson, P. J. *Drug Test. Analysis* **2014**, *6*, 24−30. (d) Mechoulam, R.; Hanus, L. O.; Pertwee, R.; Howlett, A. C. *Nat. Rev. Neurosci.* **2014**, *15*, 757−764. (e) Special issue *Nature* **2015**, *525*, S1−S18.

(2) Aizpurua-Olaizola, O.; Soydaner, U.; Öztürk, E.; Schibano, D.; Simsir, Y.; Navarro, P.; Etxebarria, N.; Usobiaga, A. *J. Nat. Prod.* **2016**, *79*, 342−331.

(3) (a) Archer, R. A.; Blanchard, W. B.; Day, W. A.; Johnson, D. W.; Lavagnino, E. R.; Ryan, C. W.; Baldwin, J. E. *J. Org. Chem.* **1977**, *42*, 2277−2284. (b) Mechoulam, R.; Lander, N.; University, A.; Zahalka, J. *Tetrahedron Asymmetry* **1990**, *1*, 315−318. (c) Burstein, S. H.; Audette, C. A.; Breuer, A.; Devane, W. A.; Colodner, S.; Doyle, S. A.; Mechoulam, R. *J. Med. Chem.* **1992**, *35*, 3135−3141.

(4) (a) Dixon, D. D.; Sethumadhavan, D.; Benneche, T.; Banaag, A. R.; Tius, M. A.; Thakur, G. A.; Bowman, A.; Wood, J. T.; Makriyannis, A. *J. Med. Chem.* **2010**, *53*, 5656−5666. (b) Gläser, F.; Bröhmer, M. C.; Hurrle, T.; Nieger, M.; Bräse, S. *Eur. J. Org. Chem.* **2015**, 1516−1524.

(5) (a) Zajicek, J.; Fox, P.; Sanders, H.; Wright, D.; Vickery, J.; Nunn, A.; Thompson, A. *Lancet* **2003**, *362*, 1517−1526. (b) Muller-Vahl, K. R.; Prevedel, H.; Theloe, K.; Kolbe, H.; Emrich, H. M.; Schneider, U. *Neuropsychopharmacology* **2003**, *28*, 384−388. (c) Mackie, K. *Annu. Rev. Pharmacol. Toxicol.* **2006**, *46*, 101−122. (d) El-Alfy, A. T.; Ivey, K.; Robinson, K.; Ahmed, S.; Radwan, M.; Slade, D.; Khan, I.; El'Sohly, M.; Ross, S. *Pharmacol. Biochem. Behav.* **2010**, *95*, 434−442. (e) Lynch, M. E.; Campbell, F. *Br. J. Clin. Pharmacol.* **2011**, *72*, 735−744.

have been described to date.[6] Cannabidiol (CBD, **2**) is another important natural cannabinoid with great potential as a drug,[7] which modulates the undesired effects of THC when used together.[8]

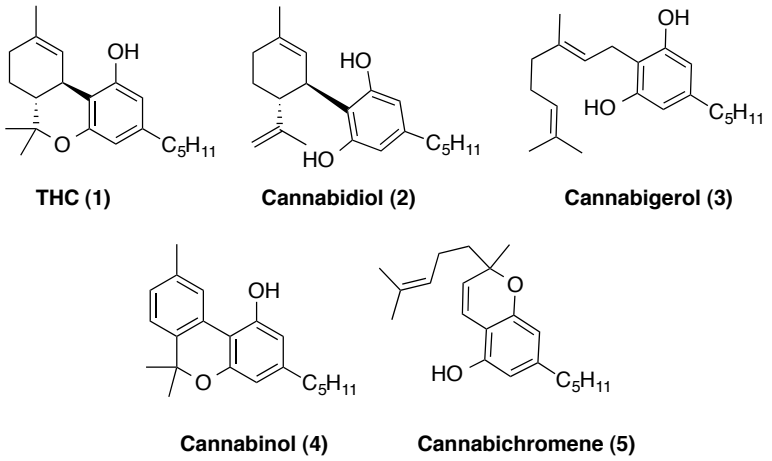


Figure 2. Phytocannabinoids

Cannabigerol (CBG, **3**) is a non-psychoactive cannabinoid typically found in low-THC strains.[9] Mechoulam and Nishioka proposed that most of the cannabinoids derive from CBG, which is converted to other types of phytocannabinoids by specialized enzymes in the plant.[10,11]

In 2010, a structurally different cannabinoid cannabimovone (**6**) was isolated from a nonpsychotropic variety of hemp (*Cannabis sativa L.*) (Figure 3).[12] This new polar cannabinoid with a rearranged 2(3→4) *abeo*-skeleton has a biological profile similar to

(6) (a) Evans, D. A.; Shaughnessy, E. A.; Barnes, D. M. *Tetrahedron Lett.* **1997**, *38*, 3193−3194. (b) Trost, B. M.; Dogra, K. *Org. Lett.* **2007**, *9*, 861−863. (c) Cheng, L.-J.; Xie, J.-H.; Chen, Y.; Wang, L.-X.; Zhou, Q.-L. *Org. Lett.* **2013**, *15*, 764−767. (d) Schafroth, M. A.; Zuccarello, G.; Krautwald, S.; Sarlah, D.; Carreira, E. M. *Angew. Chem. Int. Ed.* **2014**, *53*, 13898−13901. (e) Klotter, F.; Studer, A. *Angew. Chem. Int. Ed.* **2015**, *54*, 8547−8550.

(7) (a) Mechoulam, R.; Parker, L. A.; Gallily, R. *J. Clin. Pharmacol.* **2002**, *42*, 11S−19S. (b) Scuderi, C.; Filippis, D. D.; Iuvone, T.; Blasio, A.; Steardo, A.; Esposito, G. *Phytother. Res.* **2009**, *23*, 597−602. (c) Blessing, E.; Steenkamp, M.; Manzanares, J.; Marmar, C. *Neurotherapeutics* **2015**, *12*, 825−836.

(8) (a) Karniol, I. G.; Shirakawa, I.; Kasinski, N.; Pfeferman, A.; Carlini, E. A. *Eur. J. Pharmacol.* **1974**, *28*, 172−177. (b) Morgan, C. J. A.; Schafer, G.; Freeman, T. P.; Curran, H. V. *Br. J. Psychiatry* **2010**, *197*, 285−290. (c) Sastre-Garriga, J.; Vila, C.; Clissold, S.; Montalban, X. *Expert Rev Neurother.* **2011**, *11*, 627−637.

(9) Karniol, I. G.; Shirakawa, I.; Takahashi, R. N.; Knobel, E.; Musty, R. E. *Pharmacology* **1975**, *13*, 502–512.

(10) Traura, F.; Morimoto, S.; Shoyama, Y.; Mechoulam, R. *J. Am. Chem. Soc.* **1995**, *117*, 9766–9767.

(11) Turner, C. E.; El'Sohly, M. A.; Boeren, E. G. *J. Nat. Prod.* **1980**, *43*, 169−234.

(12) Taglialatela-Scafati, O.; Pagani, A.; Scala, F.; De Petrocellis, L.; Di Marzo, V.; Grassi, G.; Appendino, G. *Eur. J. Org. Chem.* **2010**, 2067−2072.

CBD **2**, with modest affinity for metabotropic (CB1, CB2) and relatively good activity at ionotropic (TRPV1) cannabinoid receptors.

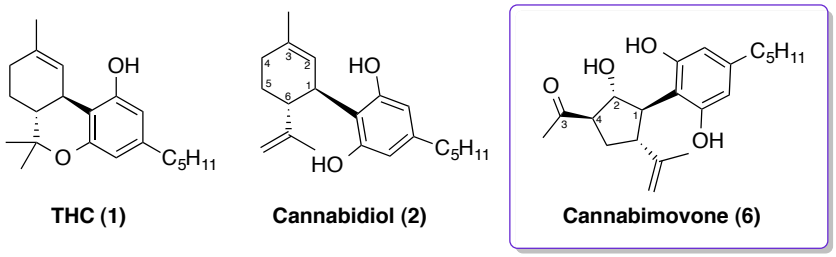
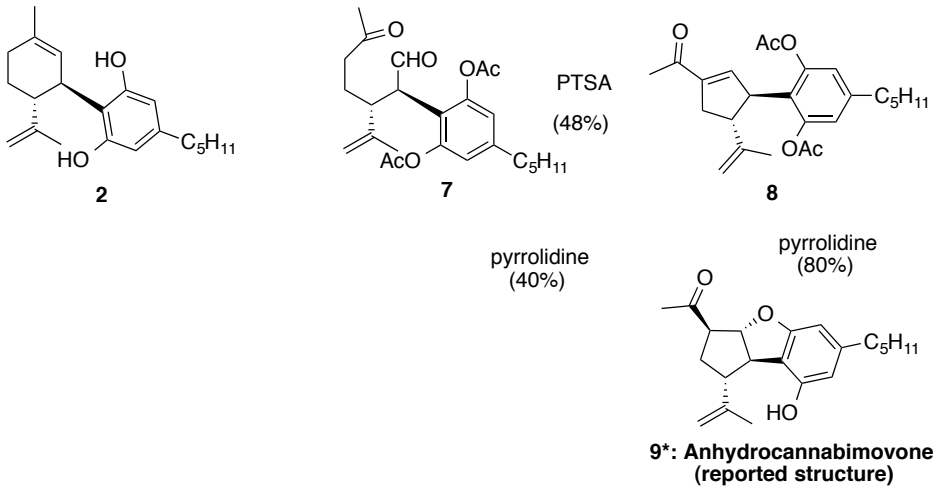


Figure 3. Natural cannabinoids THC (**1**), CBD (**2**), and cannabimovone (**6**).

The attempt of biomimetic semi-synthesis of cannabimovone **6** from CBD (**2**), reported by Taglialatela-Scafati and Appendino, relied on an intramolecular aldol reaction of ketoaldehyde **7** (Scheme 1). However, the product of dehydration **8** was obtained instead of the desired cyclopentanol **6**, when mild acidic conditions were used. Similarly, cannabimovone **6** could not be obtained under basic conditions, which led to the direct formation of the novel synthetic cannabinoid anhydrocannabimovone by an oxy-Michael addition of one of the phenol hydroxy groups to the enone. Interestingly, synthetic anhydrocannabimovone was found to exhibit a potent cannabinoid activity at CB1 and CB2 metabotropic receptors as well as at ionotropic receptors: TRPA1 channels and TRPM8. Its biological profile, to some extent, is similar to that of THC.[12]

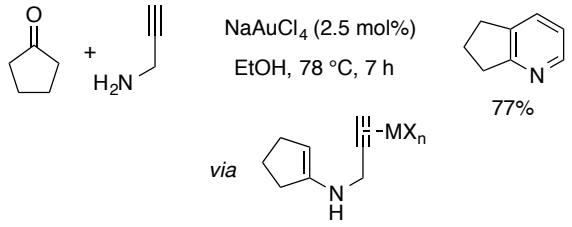


Scheme 1. Attempted biomimetic semi-synthesis of cannabimovone.

Our group developed a methodology for the gold(I)-catalyzed cycloisomerization of 1,5-enynes which allows the formation of densely functionalized cyclopentanes bearing an

isopropenyl substituent [13] presented in the structures of cannabimovone and anhydrocannabimovone.

The origin of this transformation can be traced back to the synthesis of pyridines from ketones and propargyl amines employing gold(III) catalyst, which can be considered as the first example of a gold-catalyzed cyclization of a 1,5-enyne (Scheme 2).[14]



Scheme 2. Synthesis of pyridines by cyclization of 1,5-enynes.

The 1,5-enyne cycloisomerization forming bicyclo[3.1.0]hexenes was first reported using platinum complexes,[15] although the same year gold(I) complexes were found to be more efficient catalysts for this transformation.[16] Usually, 1,5-enynes react by an *endo-dig* pathway. This can be explained by the formation of the less strained bicyclo[3.1.0]hexane system in comparison with bicyclo[2.1.0]pentane resulting from an *exo*-cyclization. However, the *exo-dig* pathway is favored when terminal alkynes or iodoalkynes are employed.[17]

The gold(I)-catalyzed cycloisomerization of 1,5-enynes gives access to a large variety of synthetically useful products (Scheme 3)[13a,18] and found its application in a field of

(13) (a) Nieto-Oberhuber, C.; Muñoz, M. P.; López, S.; Jiménez-Núñez, E.; Nevado, C.; Herrero-Gómez, E.; Raducan, M.; Echavarren, A. M. *Chem. Eur. J.* **2006**, *12*, 1677−1693. (b) López-Carrillo, V.; Huguet, N.; Mosquera, Á.; Echavarren, A. M. *Chem. Eur. J.* **2011**, *17*, 10972–10978. (c) For indene derivatives: Martínez, A.; García-García, P.; Fernández-Rodríguez, M. A.; Rodríguez, F.; Sanz, R. *Angew. Chem. Int Ed.* **2010**, *49*, 4633−4637.

(14) Abbiati, G.; Arcadi, A.; Bianchi, G.; Di Giuseppe, S.; Marinelli, F.; Rossi, E. *J. Org. Chem.* **2003**, *68*, 6959−6966.

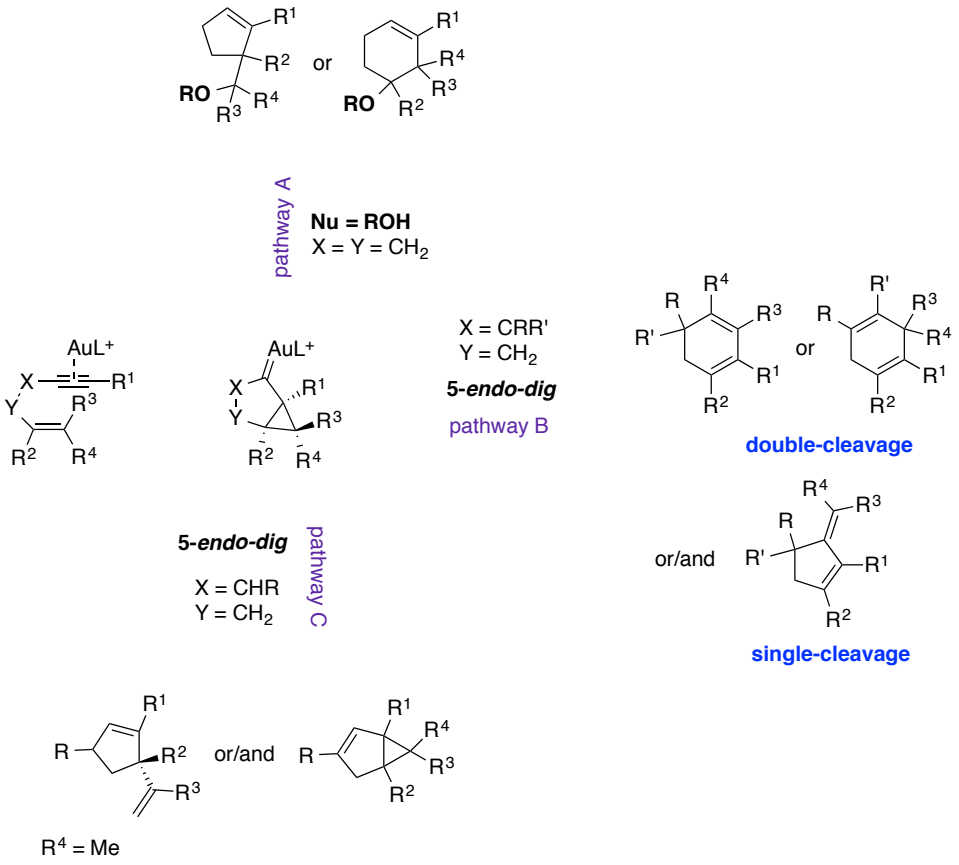
(15) (a) Mamane, V.; Gress, T.; Krause, H.; Fürstner, A. *J. Am. Chem. Soc.* **2004**, *126*, 8654−8655. (b) Harrak, Y.; Blaszykowski, C; Bernard, M.; Cariou, K.; Mainetti, E.; Mouries, V.; Dhimane, A. L.; Fensterbank, L.; Malacria, M. *J. Am. Chem. Soc.* **2004**, *126*, 8656−8657.

(16) Luzung, M. R.; Markham, J. P.; Toste, F. D. *J. Am. Chem. Soc*. **2004**, *126*, 10858−10859.

(17) Shibata, T.; Ueno, Y.; Kanda, K. *Synlett* **2006**, 4411−4414.

(18) (a) Diver, S. T.; Giessert, A. J. *Chem. Rev.* **2004**, *104*, 1317−1382. (b) Luzung, M. R.; Markham, J. P.; Toste, F. D. *J. Am. Chem. Soc.* **2004**, *126*, 10858. (c) Li, C.; Zeng, Y.; Zhang, H.; Feng, J.; Zhang, Y.; Wang, J. *Angew. Chem. Int. Ed.* **2010**, *49*, 6413−6417. (d) Dorel, R.; Echavarren, A. M. *Chem. Rev.* **2015**, *115*, 9083−9072.

product synthesis.[19,20,21] The cyclopropyl gold carbene intermediates may also undergo a formal 1,4-intermolecular addition of nucleophiles such as H_2O or alcohols to form trapping products (Scheme 3, pathway A).[22]



Scheme 3. Gold-catalyzed cycloisomerization of 1,5-enynes.

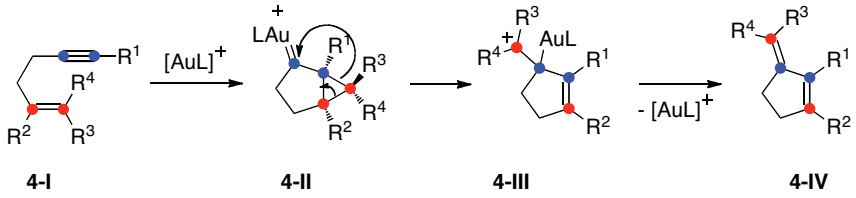
(19) Total synthesis through gold- or platinum-catalyzed cycloisomerization of 1,5-enynes: (a) Mamane, V.; Gress, T.; Krause, H.; Fürstner, A. *J. Am. Chem. Soc.* **2004**, *126*, 8654–8655. (b) Harrak, Y.; Blaszykowski, C.; Bernard, M.; Cariou, K.; Mainetti, E.; Mouris, V.; Dhimane, A.-L.; Fensterbank, L.; Malacria, M. *J. Am. Chem. Soc.* **2004**, *126*, 8656–8657. (c) Fürstner, A.; Hannen, P. *Chem. Eur. J.* **2006**, *12*, 3006–3019. (d) Fürstner, A.; Schlecker, A. *Chem. Eur. J.* **2008**, *14*, 9181–9191. (e) Lemire, G.; Gandon, V.; Cariou, K.; Hours, A.; Fukuyama, T.; Dhimane, A.-L.; Fensterbank, L.; Malacria, M. *J. Am. Chem. Soc*. **2009**, *131*, 2993–3006.

(20) Total synthesis through gold-catalyzed Conia-type cyclizations of 1,5-enynes: (a) Staben, S. T.; Kennedy-Smith, J. J.; Huang, D.; Corkey, B. K.; LaLonde, R. L.; Toste, F. D. *Angew. Chem. Int. Ed*. **2006**, *45*, 5991–5994. (b) Linghu, X.; Kennedy-Smith, J. J.; Toste, F. D. *Angew. Chem. Int. Ed.* **2007**, *46*, 7671–7673. (c) Bellavance, G.; Barriault, L. *Angew. Chem. Int. Ed.* **2014**, *53*, 6701–6704.

(21) Reviews on the application of gold catalysis to the synthesis of natural products: (a) Fürstner, A. *Chem. Soc. Rev.* **2009**, *38*, 3208–3221; (b) Rudolph, M.; Hashmi, A. S. K. *Chem. Soc. Rev.* **2012**, *41*, 2448–2462. (c) Fürstner, A. *Acc. Chem. Res.* **2014**, *47*, 925–938. (d) Zhang, Y.; Luo, T.; Yang, Z. *Nat. Prod. Rep.* **2014**, *31*, 489–503. (e) Pflästerer, D.; Hashmi, A. S. K. *Chem. Soc. Rev.* **2016**, *45*, 1331–1367.

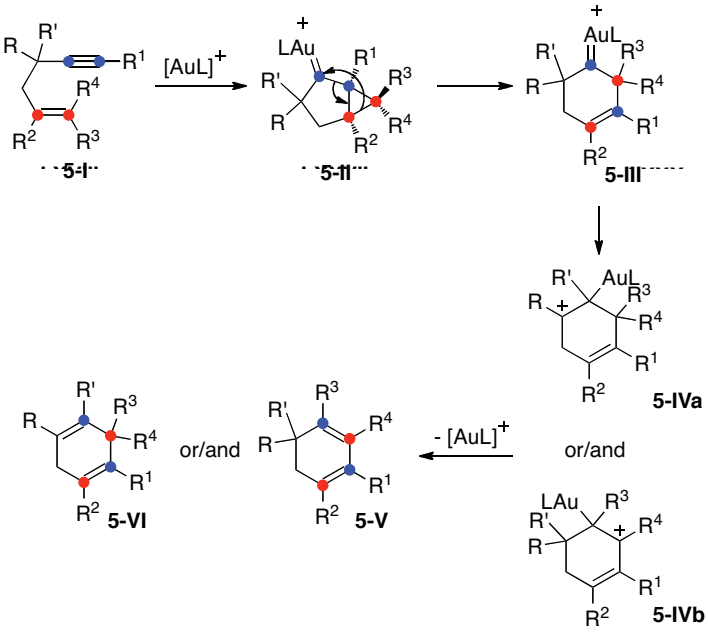
(22) Buzas, A. K.; Istrate, F. M.; Gagosz, F. *Angew. Chem. Int. Ed.* **2007**, *46*, 1141−1144.

Both, single-cleavage[23] and double-cleavage skeletal rearrangements[24] could also take place for the 1,5-enynes (Scheme 3, pathway B). The mechanism of the formation of the single-cleavage product was proposed as follows: after the attack of the alkene to the activated alkyne, the internal gold(I) carbene intermediate **4-II** can undergo a 1,2-alkyl shift to form carbocation **4-III**. Subsequent elimination of cationic gold(I) then leads to diene **4-IV** (Scheme 4).



Scheme 4. Single-cleavage skeletal rearrangement of 1,5-enynes.

The double-cleavage rearrangement in 1,5-enynes occurs by the reorganization of cyclopropyl gold(I) carbene intermediate **5-II** to form an internal gold(I) carbene (**5-III**). Then, 1,2-shift of the substituents at the α-position and demetalation would form cyclohexadienes **5-V** and **5-VI** (Scheme 5).

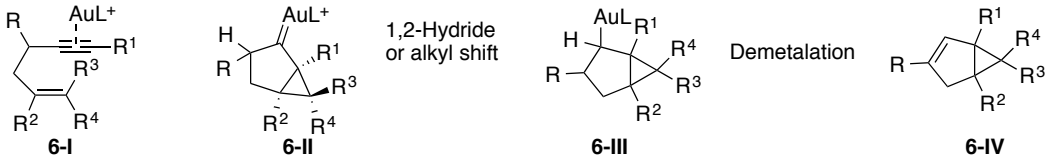


Scheme 5. Double-cleavage skeletal rearrangement of 1,5-enynes.

(23) Gagosz, F. *Org. Lett.* **2005**, *7*, 4129−4132.
(24) (a) Zhang, L.; Kozmin, S. A. *J. Am. Chem. Soc.* **2004**, *126*, 11806−11807. (b) Sun, J.; Conley, M. P.; Zhang, L.; Kozmin, S. A. *J. Am. Chem. Soc.* **2006**, *128*, 9705−9710.

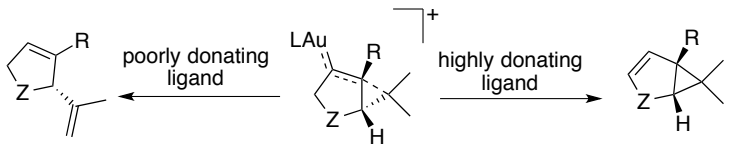
Chapter 1. Synthesis of (−)-Cannabimovone and Structural Reassignment of Anhydrocannabimovone

The 5-*endo-dig* cyclization of 1,5-enynes could also lead to the formation of functionalized bicyclo[3.1.0]hexenes and cyclopentenes bearing an isopropenyl substituent (Scheme 3, pathway C). The proposed mechanism for the formation of bicyclo[3.1.0]hexenes **6-IV** begins with the attack of the alkene to the activated alkyne in a 5-*endo-dig* manner leading to the formation of an internal cyclopropyl gold(I) carbene which further undergoes hydride or alkyl 1,2-shift to give **6-III** (Scheme 6). A final metal elimination results in the formation of the bicycle **6-IV** and regeneration of the active catalyst.



Scheme 6. The formation of bicyclo[3.1.0]hexenes *via 5-endo-dig* cyclization.

However, the selectivity of this transformation could be switched towards the preferential formation of cyclopentenes bearing an isopropenyl substituent by selecting a less donating ligand on gold (Scheme 7).[13b] Since this transformation allows the efficient generation of substituted 5-membered ring systems it could be used as a key step for the synthesis of cannabimovone **6** and anhydrocannabimovone **9**.



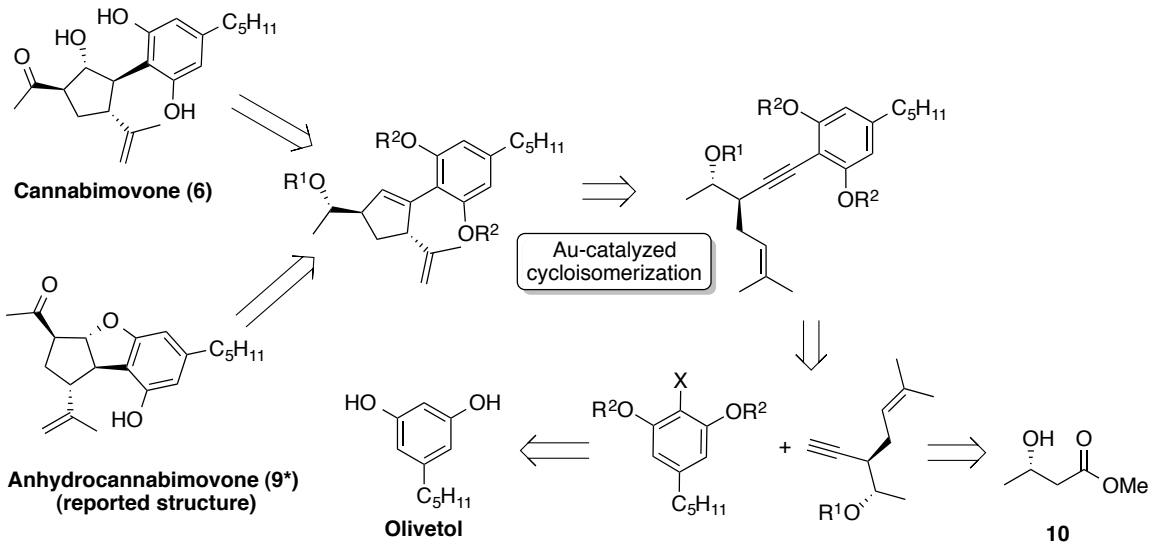
Scheme 7. Outcome of the 1,5-enyne cycloisomerization depending on the ligand used.

Chapter 1. Synthesis of (−)-Cannabimovone and Structural Reassignment of Anhydrocannabimovone

Objectives

The unprecedented *abeo*-menthane terpenoid structure of cannabimovone **6** with its densely functionalized cyclopentane with four contiguous stereocenters, coupled with its chemical lability (dehydration) under acidic and basic conditions as well as the interesting biological profiles of cannabimovone and anhydrocannabimovone, inspired us to develop a total synthesis that could allow the access to a wide variety of analogues.

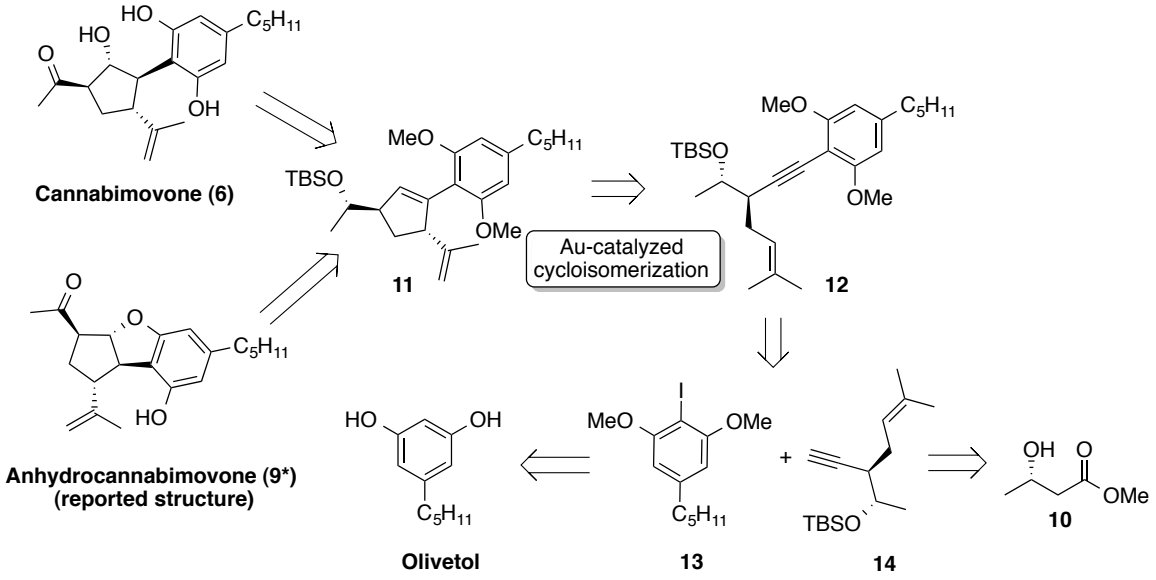
Our synthesis for these compounds would rely on a gold(I)-catalyzed cycloisomerization of an aryl-substituted 1,5-enyne, that could be obtained by cross coupling reaction between a functionalized arene and the corresponding alkyne. Both coupling partners could be easily accessible in a few steps from commercially available (+)-methyl (*S*)-3-hydroxybutyrate (**10**) and olivetol (Scheme 8).



Scheme 8. Retrosynthetic analysis for cannabimovone and anhydrocannabimovone.

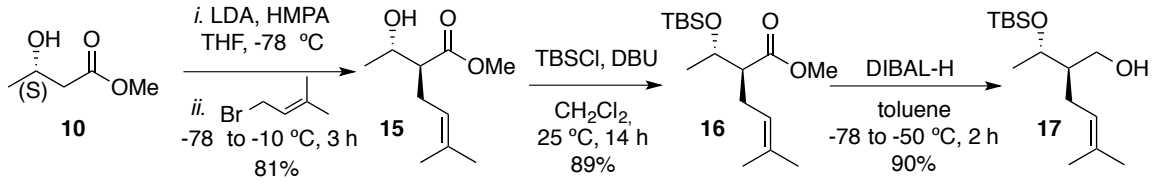
Results and discussion[25]

We envisioned to synthesize 1,5-enyne **12**, the precursor for the gold-catalyzed cycloisomerization, employing cross coupling methodology. In our first approach we selected the Sonogashira cross coupling between iodoarene **13** and alkyne **14** (Scheme 9).



Scheme 9. Retrosynthetic analysis for cannabimovone and anhydrocannabimovone.

The synthesis of the required alkyne **14** commenced by the alkylation of the lithium enolate of methyl (*S*)-3-hydroxybutanoate **10** with prenyl bromide to give known hydroxyester **15** with excellent diastereoselectivity (98 : 2) through a slight modification of the reported procedure[26] (Scheme 10). The protection of the secondary alcohol **15** as a silyl ether followed by the reduction of the ester group with DIBAL−H delivered primary alcohol **17** in 65% yield over 3 steps.

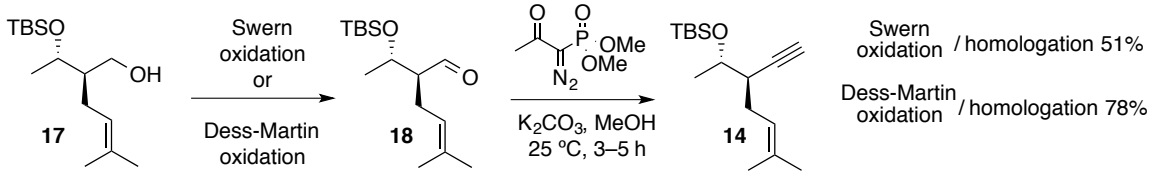


Scheme 10. Synthesis of alcohol **17**.

(25) I would like to thank Dr. Javier Carreras for developing the endocyclic olefin functionalization strategy and for the DFT calculations. I also thank and Dr. Núria Huguet and Dr. Verónica López-Carrillo for the initial 1,5-enyne cyclization studies.
(26) Koza, G.; Theunissen, C.; Al Dulayymi, J. R.; Baird, M. S. *Tetrahedron* **2009**, *65*, 10214−10229.

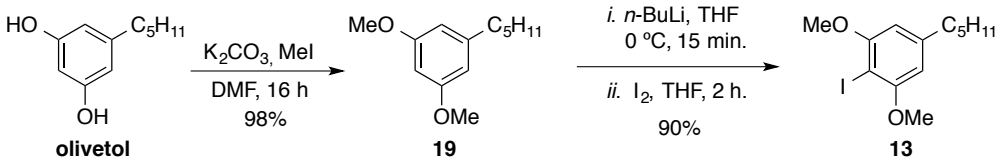
Chapter 1. Synthesis of (−)-Cannabimovone and Structural Reassignment of Anhydrocannabimovone

A two-step procedure (oxidation / homologation) provided 1,5-enyne **14** (Scheme 11). The oxidation of primary alcohol **17** with Dess-Martin periodinane followed by Seyferth-Gilbert homologation employing the Ohira-Bestmann reagent afforded the desired alkyne **14** in a 78% overall yield. When the Swern oxidation was used, alkyne **14** was obtained in 51% overall yield. Nevertheless, the Swern oxidation was selected as the method of choice during the scale-up for economical reasons. All these steps proved to be equally efficient on multi-gram scale.



Scheme 11. Synthesis of alkyne **14**.

The preparation of the arene partner **13** for the Sonogashira reaction started from olivetol. The protection of the hydroxy groups of olivetol as methyl ethers under standard conditions[27] followed by the iodination through the Snieckus *ortho*-lithiation at the 2-position of aromatic ring delivered the iodoarene **13** in a 88% yield over 2 steps (Scheme 12).



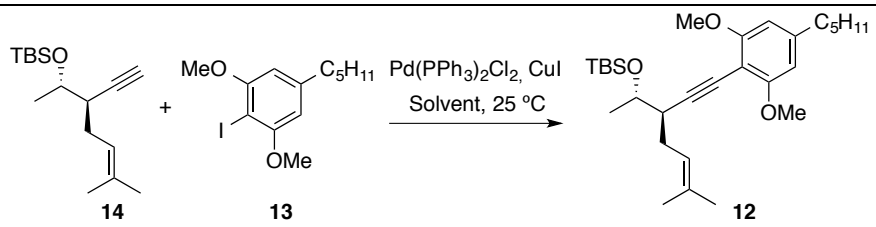
Scheme 12. Synthesis of iodoarene **13**.

The Sonogashira coupling of **14** with iodoarene **13** proved to be solvent dependent (Table 1). Only traces of the desired 1,5-enyne **12** were observed when THF was used as a co-solvent and the formation of an alkyne homocoupling product was the main pathway. Pure triethylamine and DIPEA provide the 1,5-enyne **12** in low to moderate yields, whereas a mixture of triethylamine and DIPEA in 1 : 1 ratio afforded the required Sonogashira coupling product **12** in 87% yield.

(27) Alexandros, M.; Spyridon, N. P.; Shakiru, A. O.; Vidyanand, S. G.; **Patent:** WO2009/52319, **2009**.

Chapter 1. Synthesis of (−)-Cannabimovone and Structural Reassignment of Anhydrocannabimovone

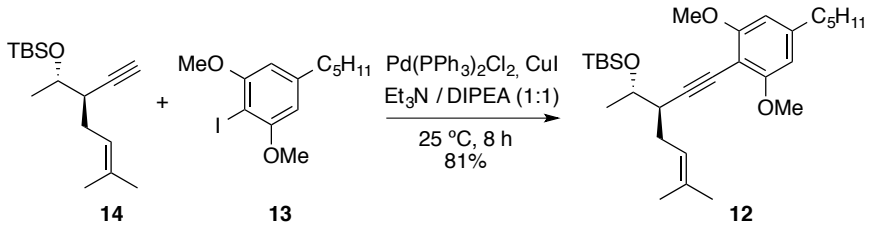
Table 1. Optimization of the Sonogashira cross-coupling reaction.



Entry	Solvent	Yield of 12, %
1	Et_3N	47
2	Et_3N / DIPEA (1 : 1)	87
3	DIPEA	24
4	Et_3N / THF (1 : 1)	traces
5	DIPEA / THF (1 : 1)	traces

Note: all reactions performed on a 0.5 mmol scale with 1.5 equiv. of alkyne **14**, 5 mol% of $Pd(PPh_3)_2Cl_2$ and 10 mol% CuI. DIPEA – diisopropylethylamine.

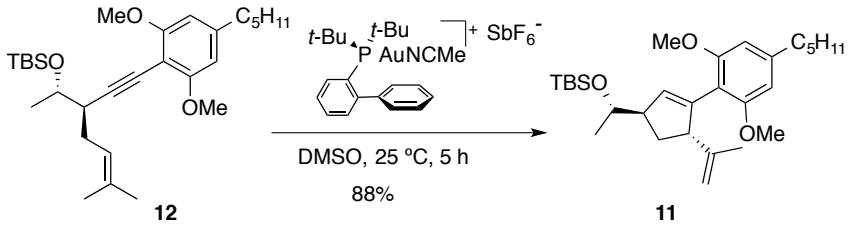
The precursor for gold-catalyzed cycloisomerization **12** was obtained in 81% yield under the optimal conditions, which was achieved by reducing the excess of alkyne **14** to 1.15 equiv (Scheme 13).



Scheme 13. Sonogashira cross coupling between iodoarene **13** and alkyne **14**.

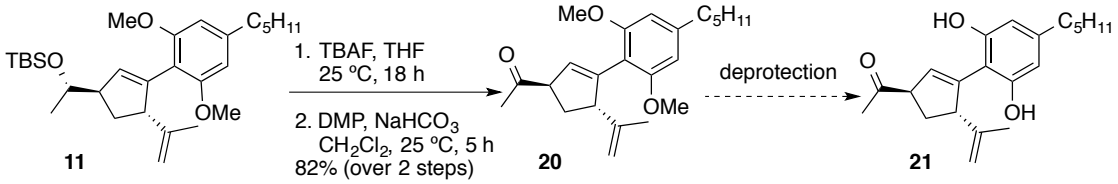
A fully diastereoselective gold(I)-catalyzed cyclization was the key step in this synthesis. This transformation would form the 5-membered ring and establish two stereogenic centers of the target molecule. We found that it proceeded efficiently with a JohnPhos cationic gold complex when DMSO was used as a solvent affording the desired polysubstituted cyclopentene **11** in 88% chemical yield (Scheme 14). The importance of this unusual choice of solvent for the gold-catalyzed cyclization will be discussed later.

Chapter 1. Synthesis of (−)-Cannabimovone and Structural Reassignment of Anhydrocannabimovone



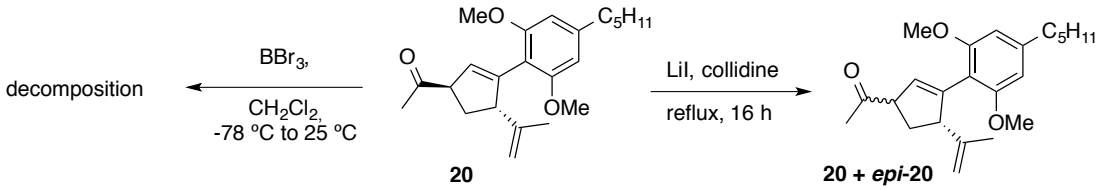
Scheme 14. Diastereoselective gold(I)-catalyzed cyclization of **12**.

The deprotection of silyl ether **11** with TBAF followed by oxidation of the secondary alcohol employing Dess-Martin periodinane afforded ketone **20** in good yield (Scheme 15). The cleavage of the methyl aryl ether would deliver the desired substrate for the devised olefin isomerization / phenol conjugate addition.



Scheme 15. Synthesis of ketone **20**.

Various methods were examined for the aryl methyl ether cleavage. The results of our extensive investigation will be briefly discussed. Standard Lewis acid deprotection methods such as TMSI[28] and BBr_3[29] led to the decomposition of the starting ketone **20** (Scheme 16). On the other hand, epimerization at the C1 position of the cyclopentene was observed when the demethylation was attempted under basic conditions using LiI in collidine.[30]

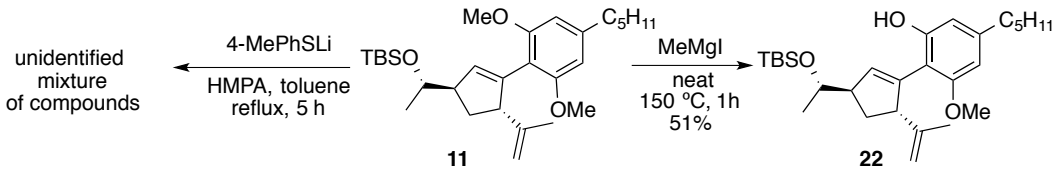


Scheme 16. Attempts of the aryl methyl ether cleavage.

To avoid epimerization, we decided to perform the aryl methyl ether cleavage on the protected secondary alcohol **11** (Scheme 17). The nucleophilic properties of 4-MePhSLi in HMPA for the deprotection of methyl ethers were reported to provide good selectivity when acidic reagents could not be used due to the presence of labile groups in the

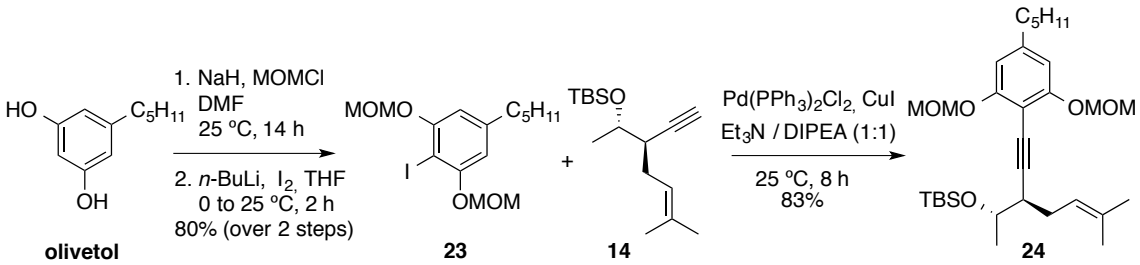
(28) Jung, M. E.; Lyster, M. A. *J. Org. Chem.* **1977**, *42*, 3761−3764.
(29) Vickery, E. H.; Pahler, L. F.; Eisenbraun, E. J. *J. Org. Chem.* **1979**, *44*, 4444−4446.
(30) Harrison, I. T. *J. Chem. Soc., Chem. Commun.* **1969**, 616a.

molecule.[31] Disappointingly, an unidentified complex mixture was obtained in the case of our substrate. However, the utilization of a large excess of *in situ* prepared methylmagnesium iodide under solvent-free conditions[32] resulted in the formation of product **22** in moderate yield. In spite of our efforts to expand this method to the double aryl methyl ether cleavage to obtain the diphenol was not succesful.



Scheme 17. Aryl methyl ether cleavage of **11**.

Since the aryl methyl ether cleavage was found to be challenging, we proposed to install methoxymethyl ether (MOM) as an alternative protecting group. The required arene partner **23** for the Sonogashira coupling was prepared in two steps from olivetol, by protection of the phenols as MOM ethers and further iodination, providing iodoarene **23** in excellent yield (80% over 2 steps) (Scheme 2). The desired 1,5-enyne **24** was obtained in 83% yield employing the previously optimized conditions for Sonogashira coupling (Scheme 18). All these steps proved to be equally efficient in a multi-gram scale.

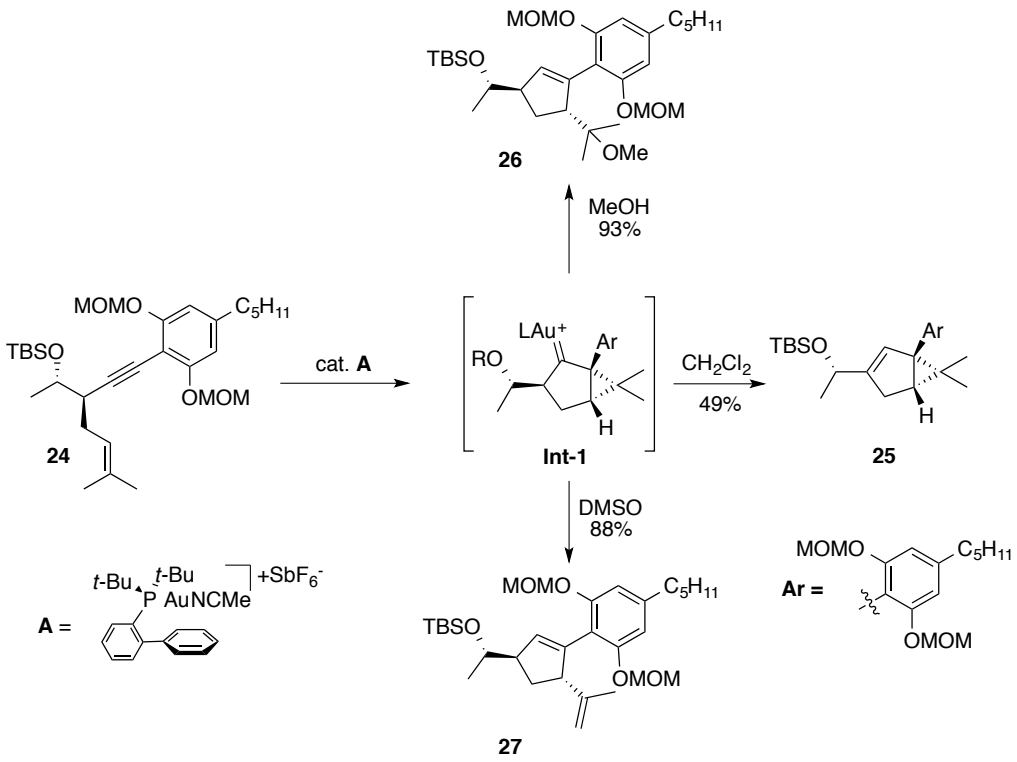


Scheme 18. Synthesis of 1,5-enyne **24**.

As was mentioned for the 1,5-enyne **12** obtained from a dimethoxyarene, the gold(I)-catalyzed cyclization of 1,5-enyne **24** proved to be highly solvent dependent. Exposing enyne **24** to the cationic gold(I) complex [(JohnPhos)Au(MeCN)]SbF_6 in CH_2Cl_2 led to the formation of fused-cyclopropane **25** in a moderate yield (Scheme 19). A similar result was obtained using other solvents such as Et_2O or THF. In the case of MeOH, only the addition product **26** was formed. However, when the reaction was performed in DMSO or

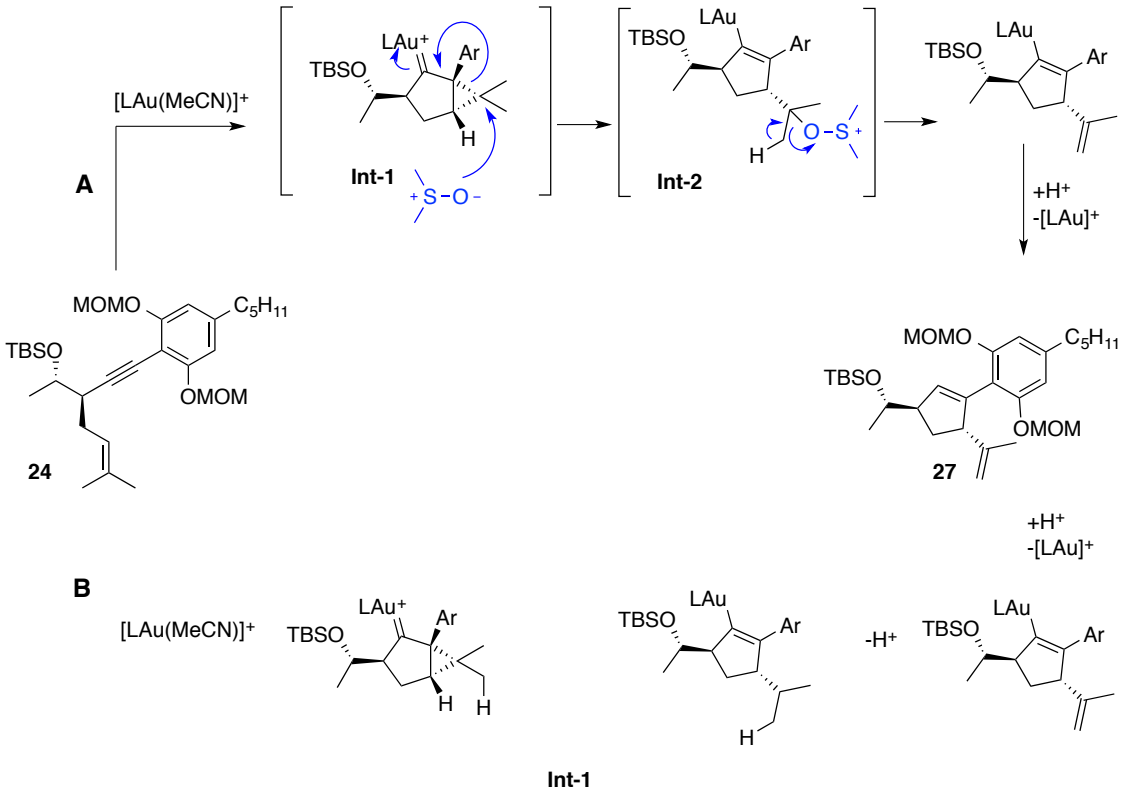
(31) Tanaka, T.; Mikamiyama, H.; Maeda, K.; Iwata, C. *J. Org. Chem.* **1998**, *63*, 9782−9793.
(32) Mechoulam, R.; Gaoni,Y. *J. Am. Chem. Soc.* **1965**, *87*, 3273−3275.

DMF, the desired cyclopentene **27** was obtained in excellent yield (88% in DMSO). Notably, the gold-catalyzed cyclization resulted in the formation of the product with the correct relative configuration, setting already two of the four final stereocenters. This reaction was performed on up to 2.10 g scale.



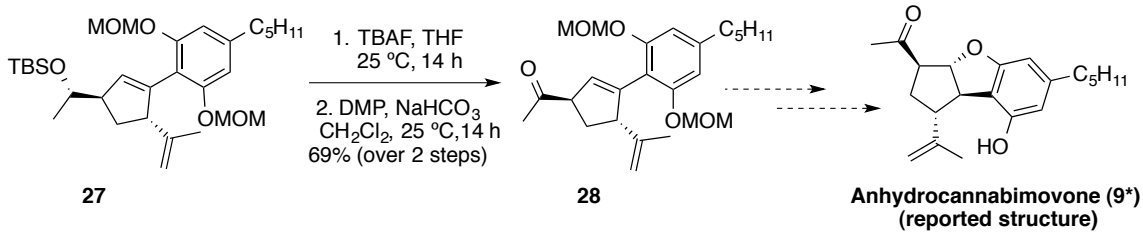
Scheme 19. Gold(I)-catalyzed cyclization of 1,5-enyne **24**.

To rationalize the solvent effect on the outcome of the reaction, we propose two possible explanations. If the reaction proceeds *via* pathway **A** (Scheme 20), then after the attack of the alkene to the activated alkyne, the initial intermediate of the gold(I)-catalyzed cyclization **Int-1** reacts with the nucleophilic solvent DMSO to form **Int-2**. An elimination and protodeauration followed by ligand exchange delivers the desired cyclopentene and closes the catalytic cycle. On the other hand, according to DFT calculations, cyclopropyl gold(I) carbene intermediate species can show either a more cationic or carbenic character depending on the substitution pattern and the nature of the ligand on gold.[13] Thus, we propose that in polar aprotic solvents such as DMSO, the intermediate of the gold(I)-catalyzed cyclization **Int-1** can follow pathway **B** losing a proton, followed by protodeauration and ligand exchange, to give rise to the desired cyclopentene.



Scheme 20. Possible mechanisms for the formation of **27**.

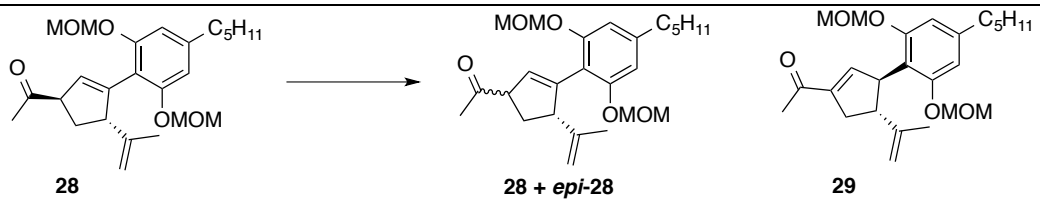
The cleavage of silyl ether **27** employing TBAF and oxidation of the secondary alcohol with Dess-Martin periodinane afforded ketone **28** in 69% yield (Scheme 21). We initially proposed that the synthesis of anhydrocannabimovone could be achieved *via* MOM deprotection and isomerization of the endocyclic olefin followed by phenol conjugate addition.



Scheme 21. Formation of ketone **28**.

Our preliminary studies, summarized in Table 2, showed that the formation of the α,β-unsaturated ketone suitable for the devised oxy-Michael addition under basic conditions was not likely to proceed satisfactorily, the epimerization at C1 being the preferential process.

Table 2. Studies of the isomerization of β,γ-unsaturated ketone **28**.

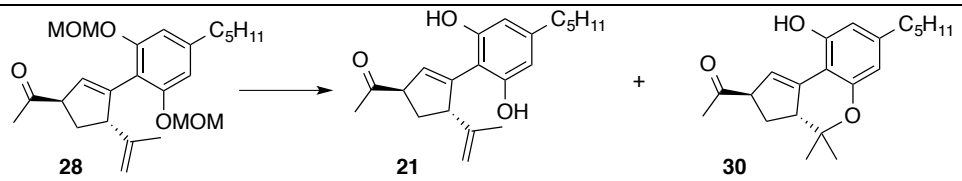


28 **28 + *epi*-28** **29**

Entry	Reagent	Solvent	Temperature, ºC	Reaction time h	Outcome
1	K_2CO_3	MeOH	25	3 h	epimerization
2	pyridine	CH_2Cl_2	55	3 h	SM
3	pyrrolidine	CH_2Cl_2	25	3 h	epimerization

Since the formation of the substrate for the designed oxy-Michael addition under basic conditions proved to be problematic, a systematic screening of Lewis and Brønsted acids, solvents and temperatures was performed in order to cleave the MOM ethers, and only selected conditions are showed in Table 3. Disappointingly, either no reaction or the decomposition of the starting ketone **28** to form complex unidentified mixtures were observed in most of the cases. The undesired tricycle **30** was obtained instead of the free phenol **21** when PTSA was used. The formation of this product can be explained by the protonation of the exocyclic olefin leading to a tertiary carbocation, which suffers an intramolecular attack by the *O*-nucleophile.

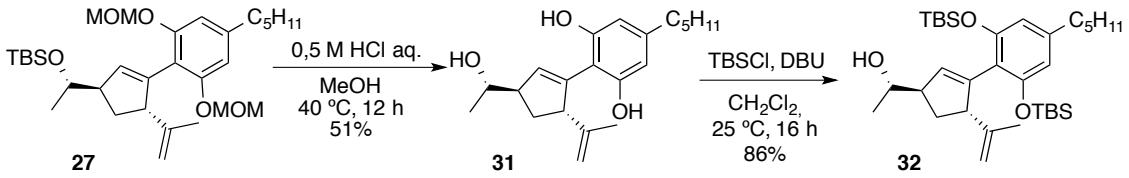
Table 3. Studies of the methoxymethyl ether **28** cleavage.



Entry	Reagent	Solvent	Temperature, °C	Reaction time h	Outcome
1	TMSBr	CH_2Cl_2	0	1.5 h	Decomposition of SM
2	HCl	*i*-PrOH	25	15 min	Decomposition of SM
3	2% H_2SO_4	MeOH/ THF	25	3 h	SM
4	CSA	MeOH	25	16 h	Complex mix
5	TFA	CH_2Cl_2	25	5 min	Decomposition of SM
6	Amberlyst	THF	45	5 h	SM
7	PTSA	acetone	50	6 h	**30**
8	PTSA	MeOH	25	16 h	**30**

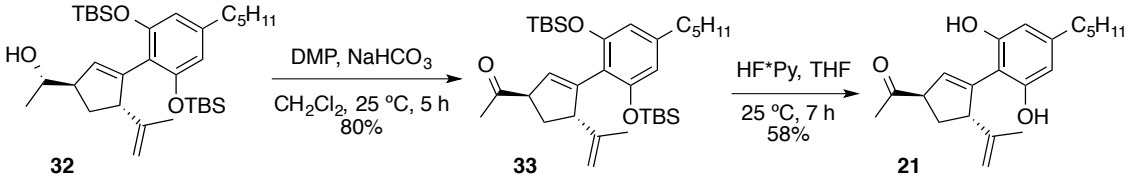
Since all the attempts to cleave the methoxymethyl ethers in ketone **28** failed, we moved back to using silyl ether **27**. Exposure of **27** to the mild acidic conditions consisting of 0.5 M aqueous HCl solution in methanol and a slightly elevated temperature led to the cleavage of both MOM and TBS protecting groups and delivered the product **31** in moderate yield (Scheme 22). The oxidation of secondary alcohol **31** in the presence of the electron-rich free phenol proved to be problematic. For this reason we protected **31** as disilyl ether under standard conditions to form **32** in 86% yield.

Chapter 1. Synthesis of (−)-Cannabimovone and Structural Reassignment of Anhydrocannabimovone



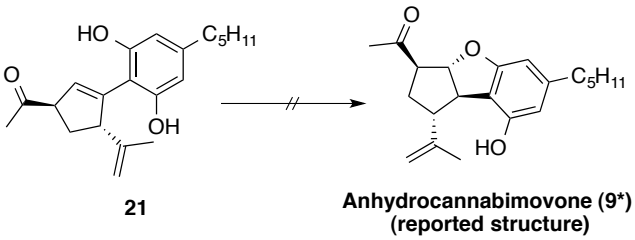
Scheme 22. Formation of the silylated phenol **32**.

Oxidation of the secondary alcohol **32** with Dess-Martin periodinane afforded ketone **33** in good yield (Scheme 23). Exposing silyl aryl ether **33** to TBAF did not provide the expected phenol **21** and the starting material was recovered intact. However, treatment with HF·Py complex gave rise to the desired substrate **21** for the devised olefin isomerization / phenol conjugate addition in 58% yield.



Scheme 23. Synthesis of ketone **21**.

Various bases were tested to promote the olefin isomerization / oxy-Michael addition such as DBU, pyrrolidine, DIPEA, NaOMe, phosphazene base P1-*t*-Bu-tris(tetramethylene) and NaH. However, the cyclization failed, leading instead to decomposition or epimerization of the starting material.

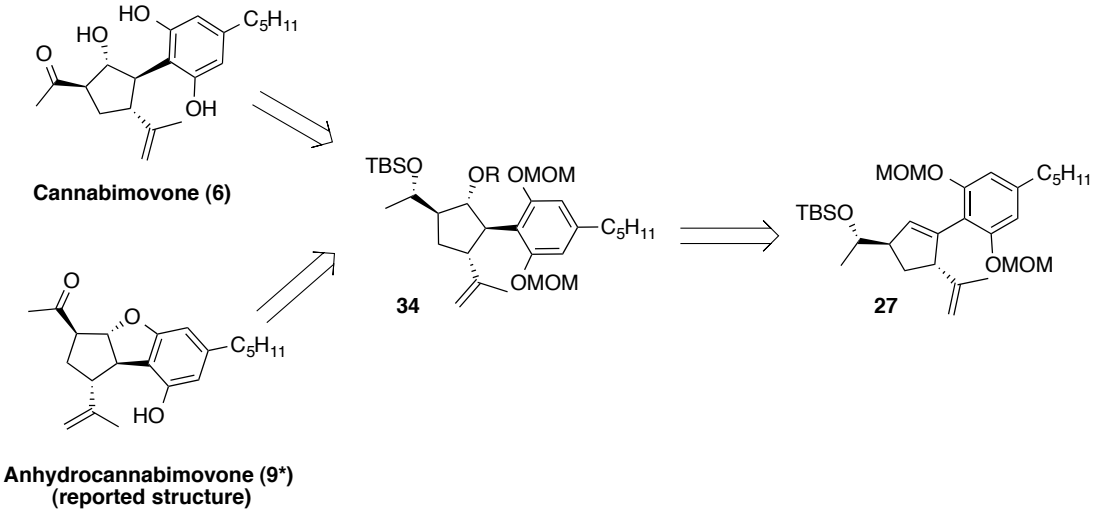


Scheme 24. Studies towards the synthesis of anhydrocannabimovone.

At that point we focused our attention on the functionalization of the endocyclic double bond since the olefin isomerization / oxy-Michael addition strategy proved to be problematic.

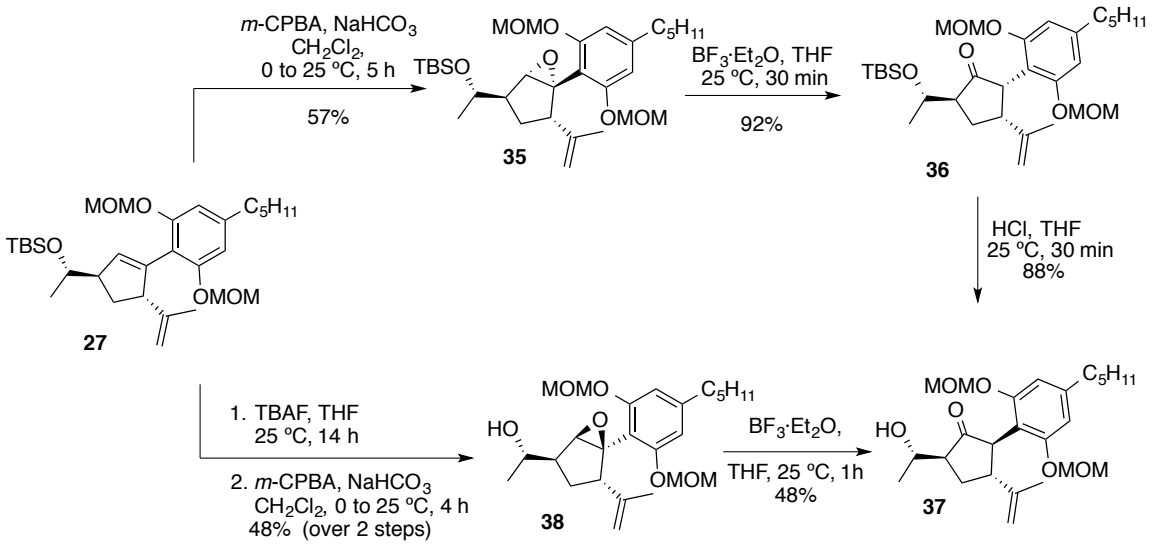
Chapter 1. Synthesis of (−)-Cannabimovone and Structural Reassignment of Anhydrocannabimovone

As previously mentioned, the late stage olefin isomerization / oxy-Michael addition strategy failed. We proposed that the functionalization of the internal olefin after the gold-catalyzed cycloisomerization followed by functional group modifications would give us access to cannabimovone and anhydrocannabimovone (Scheme 25).



Scheme 25. New retrosynthetic approach.

To introduce the desired functionality on the five-membered ring, we examined the hydroboration, nitration and hydrosilylation of the endocyclic alkenes, which failed. To our delight, a Prilezhaev epoxidation employing *m*-CPBA and $NaHCO_3$ led to the exclusive formation of the desired oxirane **35** (Scheme 26). A Meinwald rearrangement with a stoichiometric amount of Lewis acid such as $BF_3{\cdot}Et_2O$ provided ketone **36** (2,3-*cis*). Epimerization and simultaneous silyl ether deprotection were achieved by exposure of **36** to an aqueous solution of hydrochloric acid, affording hydroxyketone **37**. The relative configuration of cyclopentanone **37** was confirmed by NMR studies and additionally by its preparation through an alternative pathway. Thus, the cleavage of TBS silyl ether **27** with TBAF, followed by epoxidation provided oxirane **38** in 48% overall yield. The Meinwald rearrangement of hydroxyepoxide **38** with $BF_3{\cdot}Et_2O$ delivered β-hydroxyketone **37** in moderate yield.

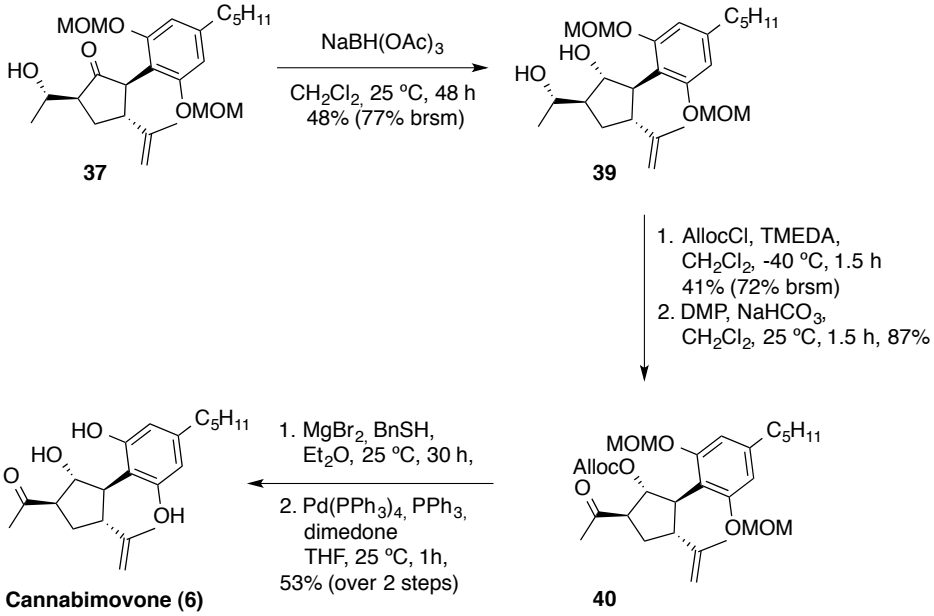


Scheme 26. Synthesis of β-hydroxy ketone **37**.

The diastereoselective reduction of β-hydroxyketone **37** under Saksena-Evans conditions[33] employing $NaBH(OAc)_3$ in CH_2Cl_2 gave diol **39** (Scheme 27). The mono Alloc protection of cyclopentanol **39** proceeded with moderate regioselectivity and required accurate temperature control to avoid the formation of the bisacylated product. Protected cannabimovone **40** was obtained by the oxidation of the free secondary alcohol with Dess-Martin periodinane. The cleavage of the methoxymethyl ether using $MgBr_2$ and BnSH,[34] followed by Pd(0)-catalyzed deprotection of the allyl carbonate provided cannabimovone **6** (53% over 2 steps). The spectral data and optical rotation of synthetic cannabimovone (**6**) matched those reported for the natural compound (optical rotation of synthetic **6** $[a]_D^{22} = -6.8º$ (c = 0.70, $CHCl_3$), reported $[a]_D^{22} = -10º$ (c = 0.07, $CHCl_3$)).[12]

(33) (a) 1,3-Directed reductions with $NaBH_4$ / AcOH: Saksena, A. K.; Mangiaracina, P. *Tetrahedron Lett.* **1983**, *24*, 273−276. (b) Optimisation and utility in polyketide synthesis: Evans, D. A.; Chapman, K. T.; Carreira, E. M. *J. Am. Chem. Soc.* **1988**, *110*, 3560−3578.
(34) (a) Kim, S.; Kee, I. S.; Park, Y. H.; Park, J. H. *Synlett* **1991**, 183−184; (b) Kim, W. H.; Angeles, A. R.; Lee, J. H.; Danishefsky, S. J. *Tetrahedron Lett.* **2009**, *50*, 6440–6441.

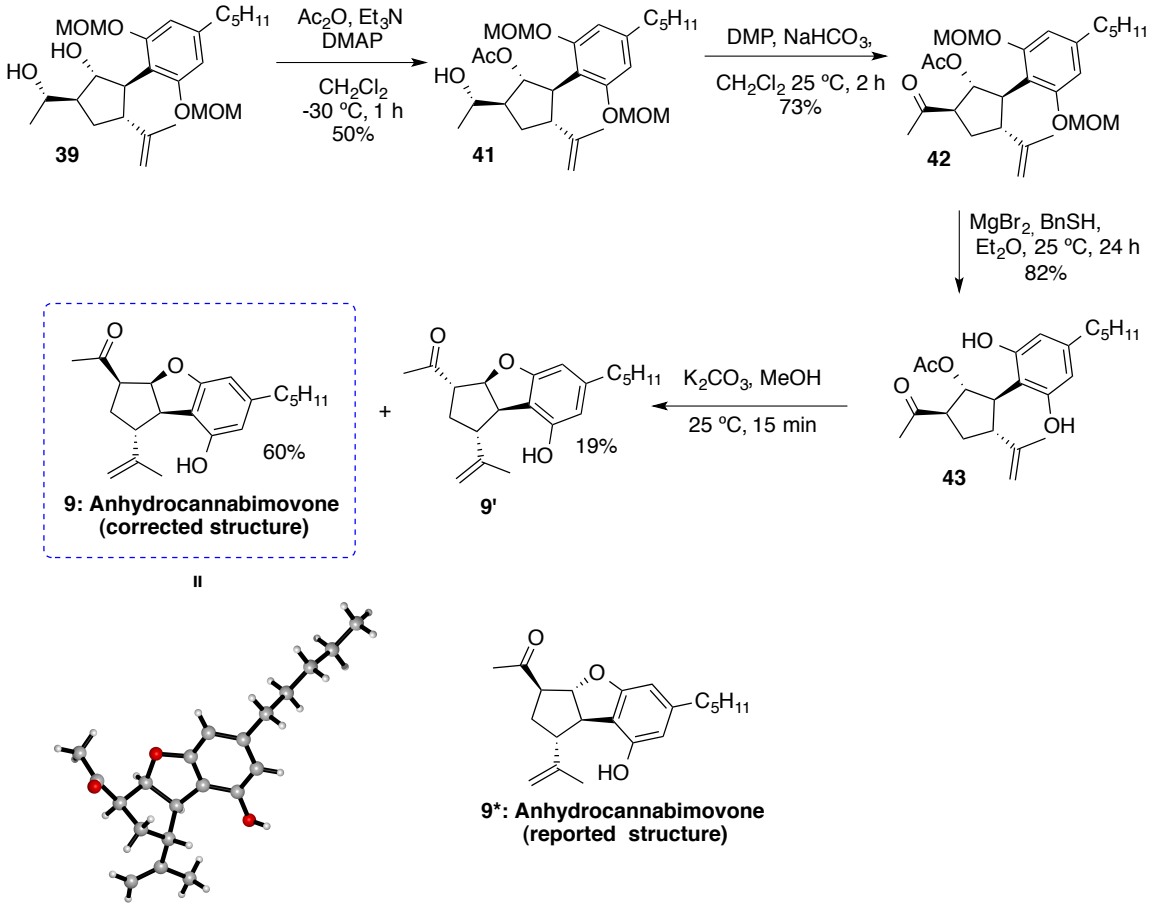
Chapter 1. Synthesis of (−)-Cannabimovone and Structural Reassignment of Anhydrocannabimovone



Scheme 27. Synthesis of cannabimovone **6**.

The synthesis of anhydrocannabimovone (**9**) was carried out from diol **39** (Scheme 28). Diol **39** was protected as monoacetate **41**. Further oxidation of the secondary alcohol **41** with Dess-Martin periodinane and cleavage of the methoxymethyl ether afforded acetylcannabimovone **43** in 30% yield from **39**. The exposure of **43** to basic conditions resulted in the formation of anhydrocannabimovone (**9**) and *epi*-anhydrocannabimovone (**9'**) in a 3 : 1 ratio.

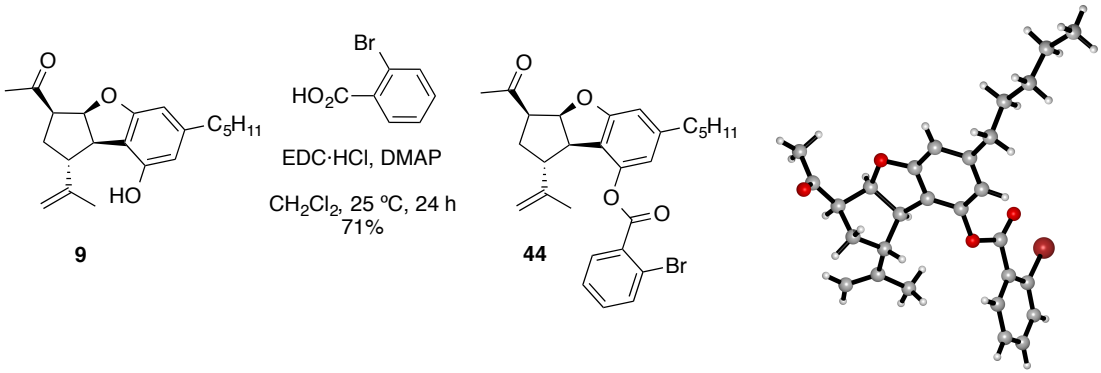
Chapter 1. Synthesis of (−)-Cannabimovone and Structural Reassignment of Anhydrocannabimovone



Scheme 28. Synthesis and X-ray crystal structure of anhydrocannabimovone **9**.

Although the ^{1}H NMR of the major isomer **9** was identical to that reported for anhydrocannabimovone, very significant differences were observed in the ^{13}C NMR spectrum. Furthermore, the optical rotation of **9** ($[a]_D^{22}$ = +40.6º (c = 0.29, $CHCl_3$)) differed much from the one reported ($[a]_D^{22}$ = −17º (c = 0.02, $CHCl_3$))[12]. However, to remove any doubt on the structure of our synthetic material, the structure and relative configuration of anhydrocannabimovone (**9**) were confirmed by X-ray diffraction and its absolute configuration was assigned on the basis of the X-ray structure of anhydrocannabimovone 2-bromobenzoate **44** (Scheme 29).

Chapter 1. Synthesis of (−)-Cannabimovone and Structural Reassignment of Anhydrocannabimovone



Scheme 29. Synthesis of anhydrocannabimovone 2-bromobenzate **44**. X-ray structure.

In order to clarify the discrepancy between our structural assignment and that originally reported, we performed DFT calculations to study the oxy-Michael cyclization. Under basic conditions, the oxy-Michael cyclization of the phenolate anion should lead to the *cis* fusion, which is more favored than the *trans* addition by *ca.* 20 Kcal·mol^{-1} (Figure 4).[35]

(35) Gordon, H. L.; Freeman, S.; Hudlicky, T. *Synlett* **2005**, *19*, 2911−2914.

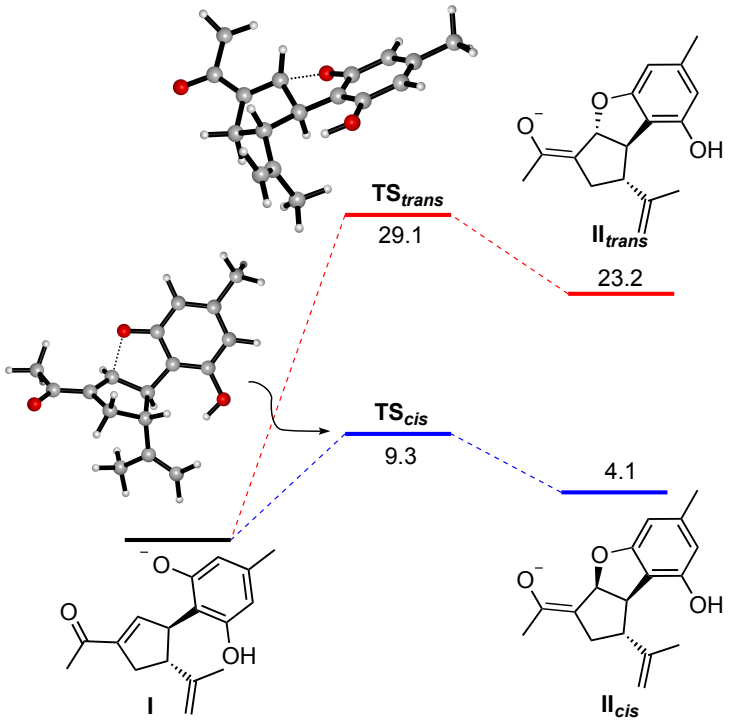


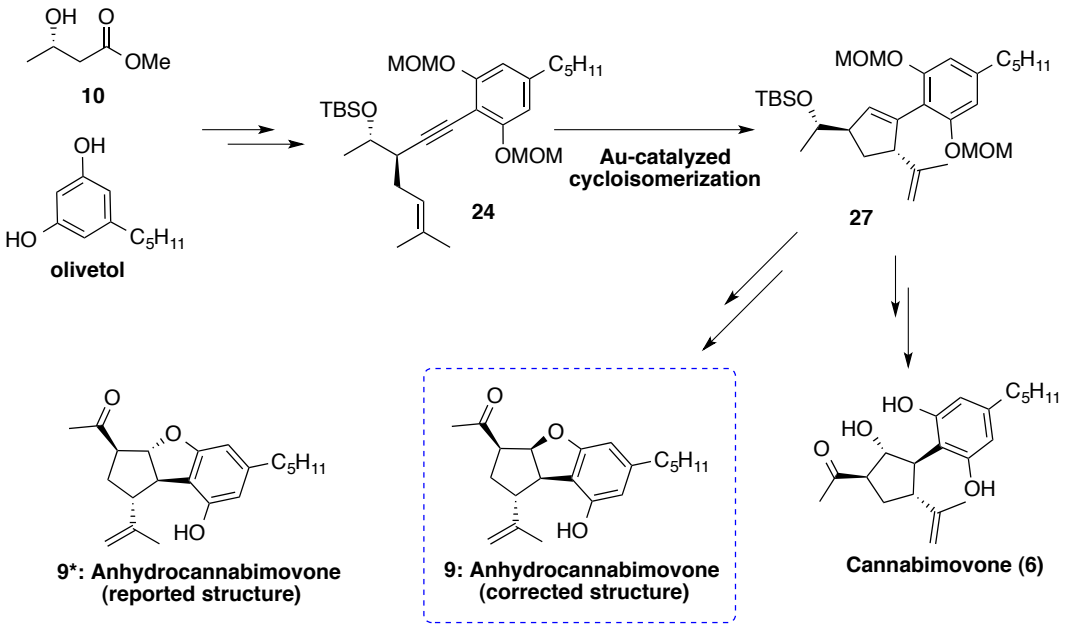
Figure 4. Energy profile (*cis* and *trans*) for the oxy-Michael cyclization. DFT calculations (M06-2x/6-31G(d,p) (MeOH), ΔG (kcal·mol^{-1}).

Furthermore, DFT calculations were employed to predict the expected ^{13}C NMR chemical shifts of the different possible products.[36] Our data of anhydrocannabimovone (**9**), as well as the reported data for **9***, were in better agreement with the *cis*-tetrahydro-1*H*-cyclopenta[*b*]benzofuran structure **9**.

(36) (a) Lodewyk, M. W.; Siebert, M. R.; Tantillo, D. J. *Chem. Rev.* **2012**, *112*, 1839–1862. Some recent examples: (b) White, K. N.; Amagata, T.; Oliver, A. G.; Tenney, K.; Wenzel, P. J.; Crews, P. *J. Org. Chem.* **2008**, *73*, 8719–8722. (c) Hu, G.; Liu, K.; Williams, L. J. *Org. Lett.* **2008**, *10*, 5493−5496. (d) Li, Y. *RSC Adv.* **2015**, *5*, 36858–36864.

Conclusions

In conclusion, we accomplished the first total synthesis of (-)-cannabimovone (**6**). The key step of this asymmetric synthesis is a fully diastereoselective gold(I)-catalyzed cyclization that efficiently formed the five member ring. Starting from one stereogenic center present in commercially available (+)-methyl (*S*)-3-hydroxybutyrate (**10**), the four stereogenic centers of the target molecule were established. Interestingly, this is the first application of the cycloisomerization of simple 1,5-enynes in the context of natural product synthesis. We also synthesized anhydrocannabimovone (**9**) and revised the configuration of the ring fusion by X-ray crystallography and DFT calculations. This synthetic sequence provides ready access to cannabimovone **6** and anhydrocannabimovone **9**, as well as other synthetic cannabinoids for biological testing. Biological testing of these and related compounds against cannabinoid receptors is in progress.



Scheme 30. Synthesis of cannabimovone **6** and anhydrocannabimovone **9**.

Experimental section

General Information

Unless otherwise stated, reactions were carried out under argon atmosphere in solvents dried by passing through an activated alumina column on a PureSolv^{TM} solvent purification system (Innovative Technologies, Inc., MA). Analytical thin layer chromatography was carried out using TLC-aluminium sheets with 0.2 mm of silica gel (Merck GF_{234}) using UV light as the visualizing agent and an acidic solution of vanillin or anisaldehyde in ethanol as the developing agent. Chromatographic purifications were carried out using flash grade silica gel (SDS Chromatogel 60 ACC, 40-63 mm), neutral aluminium oxide (SDS, 63-200 μm) or basic aluminium oxide (SDS, 50-200 μm). Organic solutions were concentrated under reduced pressure on a Büchi rotary evaporator.

NMR spectra were recorded at 298 K (unless otherwise stated) on a Bruker Avance 300, Bruker Avance 400 Ultrashield and Bruker Avance 500 Ultrashield apparatuses. The signals are given as d / ppm (multiplicity, coupling constant (Hertz), number of protons) downfield from tetramethylsilane, with calibration on the residual protio-solvent used (d_H = 7.27 ppm and d_C = 77 ppm for $CDCl_3$, d_H = 5.32 ppm and d_C = 53.84 ppm for CD_2Cl_2). Mass spectra were recorded on a Waters Micromass LCT Premier (ESI), Waters Micromass GCT (EI, CI) and Bruker Daltonics Autoflex (MALDI) spectrometers. Melting points were determined using a Büchi melting point apparatus.

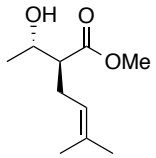
Crystal structure determinations were carried out using a Bruker-Nonius diffractomer equipped with an APPEX 2 4K CCD area detector, a FR591 rotating anode with MoK_a radiation, Montel mirrors as monochromator and a Kryoflex low temperature device (T = –173 ºC). Full-sphere data collection was used with w and j scans. *Programs used*: Data collection APEX-2, data reduction Bruker Saint V/.60A and absorption correction SADABS. Structure Solution and Refinement: Crystal structure solutions were achieved using direct methods as implement in SHELXTL and visualized using the program XP. Missing atoms were subsequently located from difference Fourier synthesis and added to the atom list. Least-squares refinement on F2 using all measured intensities was carried out using the program SHELXTL. All non-hydrogen atoms were refined including anisotropic displacement parameters.

Chapter 1. Synthesis of (−)-Cannabimovone and Structural Reassignment of Anhydrocannabimovone

HPLC analysis was carried out on an Agilent Technologies instrument HPLC 1100 series with VWD detector or HPLC 1200 series with DAD detector.

All reagents were used as purchased and used with no further purification, unless otherwise stated.

(*S*)-Methyl 2-((*S*)-1-hydroxyethyl)-5-methylhex-4-enoate (15)

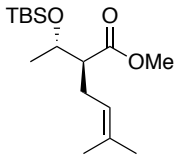


LDA was prepared by adding *n*-BuLi (32.0 mL, 80.0 mmol, 2.5 M in hexanes, 2 equiv) to a solution of diisopropylamine (11.2 mL, 80.0 mmol, 2 equiv) in 60 mL of THF, at 0 °C under inert atmosphere. The solution was stirred 30 min at 0 °C and then cooled to –70 °C. (+)-Methyl (*S*)-3-hydroxybutyrate **10** (4.5 mL, 40.0 mmol, 1 equiv) in THF (30 mL) was added to the LDA solution at -70 ºC and stirred for 1 h. The reaction mixture was allowed to warm up to -10 ºC (45 min) and recooled to -70 ºC for the addition of HMPA (14 mL, 80 mmol, 2 equiv) and 3,3-dimethylallylbromide (7.0 mL, 60.0 mmol, 1.5 equiv) in THF (10 mL). The reaction mixture was allowed to warm up to -10 ºC and stirred in total for 3 h. The reaction was treated with saturated solution of NH_4Cl (50 mL) and the aqueous phase was extracted with Et_2O (2 × 30 mL). The combined organic phases were dried over Na_2SO_4. Column chromatography (cyclohexane / EtOAc, 9 : 1) yielded alcohol **15** (6 g, 32.4 mmol, 81%) as a colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.08 − 5.00 (m, 1H), 3.90 (h, *J* = 6.4 Hz, 1H), 3.68 (s, 2H), 2.62 (d, *J* = 7.3 Hz, 1H), 2.44 − 2.28 (m, 4H), 1.67 (d, *J* = 1.5 Hz, 2H), 1.60 (d, *J* = 1.1 Hz, 1H), 1.21 (d, *J* = 6.4 Hz, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 175.7, 134.4, 120.4, 67.9, 52.8, 51.7, 28.1, 25.9, 21.7, 17.8. **HRMS-ESI** *m/z* calcd for $C_{10}H_{18}O_3Na$ $[M+Na]^+$ 209.1154, found 209.1158. $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{25}}$ = −6.8º (c = 0.98, $CHCl_3$).

Previously reported procedure.[26] NMR data were in accordance with those previously reported for (*R*)-1, $[\alpha]_D^{20}$ = +7.2º (c = 1.05, $CHCl_3$).[37]

(*S*)-Methyl 5-methyl-2-((*S*)-1-((*tert*-butyldimethylsilyl)oxy)ethyl)hex-4-enoate (16)

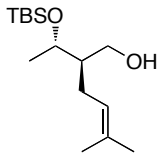


DBU (4.9 mL, 33.1 mmol, 1.1 equiv) and TBSCl (4.76 g, 31.6 mmol, 1.05 equiv) were added to a solution of **15** (5.6 g, 30.1 mmol, 1 equiv) in CH_2Cl_2 (50 mL) at 0 ºC under argon atmosphere. The reaction was stirred for 16 h at 25 ºC. The mixture was quenched with 10% HCl solution (30 mL) and the aqueous phase was extracted with CH_2Cl_2 (2 × 15 mL). The combined organic phases were washed with brine, dried over Na_2SO_4 and purified by column chromatography (hexane / EtOAc, 25 : 1) to give ester **16** (8.0 g, 26.79 mmol, 89%) as a colourless oil.

(37) Kramer, A.; Pfander, H. *Helv. Chim. Acta* **1982**, 65, 293−301.

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.06 − 5.00 (m, 1H), 4.00 (dq, *J* = 7.4, 6.2 Hz, 1H), 3.63 (s, 3H), 2.40 (ddd, *J* = 10.4, 7.3, 4.4 Hz, 1H), 2.29 − 2.21 (m, 1H), 2.17 − 2.10 (m, 1H), 1.66 (s, 3H), 1.59 (s, 3H), 1.16 (d, *J* = 6.2 Hz, 3H), 0.85 (s, 9H), 0.05 (s, 3H), 0.02 (s, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 174.8, 133.5, 121.2, 69.8, 55.0, 51.4, 27.0, 25.9, 25.9, 21.5, 18.0, 17.8, −4.1, −5.0. **HRMS-ESI** *m/z* calcd for $C_{16}H_{32}O_3NaSi$ $[M+Na]^+$ 323.2018, found 323.2031. $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{25}}$ = +12.7º (c = 0.95, $CHCl_3$).

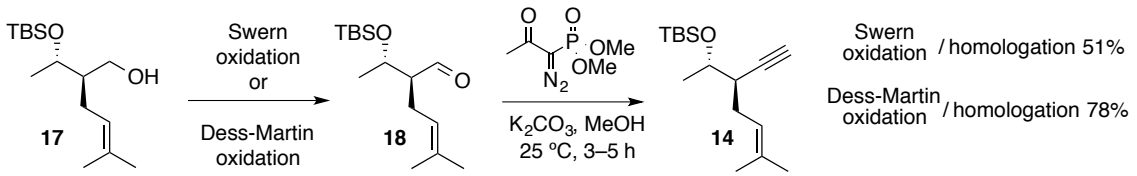
(*R*)-5-Methyl-2-((*S*)-1-((*tert*-butyldimethylsilyl)oxy)ethyl)hex-4-en-1-ol (17)



A solution of DIBAL-H (50.6 mL, 50.6 mmol, 1M in hexane, 2 equiv) was added to a stirred solution of methyl ester **16** (7.6 g, 25.3 mmol, 1 equiv) in toluene (50 mL) at −78 ºC under argon atmosphere. The reaction was allowed to warm up to −50 ºC and stirred for 2 h. A second portion of DIBAL-H (50.6 mL, 50.6 mmol, 1M in hexane, 2 equiv) was added and stirred for additional 2 h at −50 ºC. The mixture was quenched with Rochelle solution (*ca* 150 mL), stirred for 1 h and the aqueous phase was extracted with Et_2O (3 × 40 mL). The combined organic phases were dried over Na_2SO_4 and purified by column chromatography (hexane / EtOAc, 10 : 1) to give alcohol **17** (5.8 g, 21.25 mmol, 84%) as a colourless oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.14 (ddt, *J* = 7.9, 6.6, 1.4 Hz, 1H), 3.96 (qd, *J* = 6.3, 4.0 Hz, 1H), 3.90 (ddd, *J* = 11.2, 3.8, 2.8 Hz, 1H), 3.59 − 3.53 (m, 1H), 3.00 (dd, *J* = 7.3, 3.7 Hz, 1H), 2.20 (dt, *J* = 15.8, 8.3 Hz, 1H), 2.05 (dt, *J* = 13.5, 6.1 Hz, 1H), 1.70 (d, *J* = 1.3 Hz, 3H), 1.62 (s, 3H), 1.38 (dt, *J* = 8.9, 3.5 Hz, 1H), 1.25 (d, *J* = 6.3 Hz, 3H), 0.89 (s, 9H), 0.09 (s, 6H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 133.2, 122.7, 72.9, 63.0, 47.2, 27.9, 25.9, 22.5, 18.0, 18.0, −4.1, −4.9. **HRMS-ESI** *m/z* calcd for $C_{15}H_{32}O_2NaSi$ $[M+Na]^+$ 295.2069, found 295.2060. $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{25}}$ = +12.8º (c = 1.07, $CHCl_3$).

(((2*S*,3*R*)-3-Ethynyl-6-methylhept-5-en-2-yl)oxy) *tert*-butyldimethylsilane (14)



DMSO (1.9 mL, 26.4 mmol, 2.4 equiv) was added to a solution of oxalyl chloride (0.9 mL, 11.0 mmol, 1 equiv) in CH_2Cl_2 (50 mL) at −60 ºC under argon atmosphere and stirred for 10 min. Then a solution of alcohol **17** (3 g, 11.0 mmol, 1 equiv) in CH_2Cl_2

(20 mL) was added and stirred for 15 min. After addition of Et_3N (8.4 mL, 60.5 mmol, 5.5 equiv) the reaction mixture was stirred at 25 ºC for 1 h. The reaction was quenched with 10% HCl solution (30 mL) and after extractive work up (CH_2Cl_2), aldehyde **18** was isolated as colourless oil and used without further purification.

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.68 (d, *J* = 3.1 Hz, 1H), 5.05 (m, 1H), 4.17 − 4.00 (m, 1H), 2.44 (dd, *J* = 14.9, 8.9 Hz, 1H), 2.28 − 2.12 (m, 2H), 1.67 (s, 3H), 1.61 (s, 4H), 1.22 (d, *J* = 6.3 Hz, 3H), 0.87 (s, 9H), 0.06 (s, 6H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 205.5, 133.9, 120.8, 69.0, 59.8, 25.9, 25.9, 25.8, 25.2, 22.4, 18.0, −4.0, −4.9.

Dimethyl (1-diazo-2-oxopropyl)phosphonate (2.5 g, 13.2 mmol, 1.2 equiv) and K_2CO_3 (3.1 g, 22.0 mmol, 2 equiv) were added to a solution of aldehyde **18** in MeOH (15 mL) at 0 ºC under argon atmosphere and the reaction mixture was stirred for 5 h at 25 ºC. The solvent was evaporated and extractive work-up (CH_2Cl_2 / H_2O) was performed. The combined organic phases were washed with brine, dried over Na_2SO_4 and purified by column chromatography (hexane / EtOAc, 20 : 1) to give alkyne **14** (1.5 g, 5.61 mmol, 51%) as a colourless oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.26 (ddt, *J* = 8.4, 5.5, 1.5 Hz, 1H), 3.93 (qd, *J* = 6.2, 3.9 Hz, 1H), 2.39 − 2.27 (m, 2H), 2.17 − 2.09 (m, 1H), 2.04 (d, *J* = 2.4 Hz, 1H), 1.72 (d, *J* = 1.4 Hz, 3H), 1.63 (s, 1H), 1.21 (d, *J* = 6.2 Hz, 3H), 0.90 (s, 9H), 0.07 (s, 3H), 0.06 (s, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 133.1, 122.2, 85.7, 70.4, 69.7, 40.7, 28.1, 26.0, 26.0, 20.3, 18.2, 18.1, −4.3, −4.7. **HRMS-ESI** *m/z* calcd for $C_{16}H_{30}ONaSi$ $[M+Na]^+$ 289.1964, found 289.1964. $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{25}}$ = −32.5º (c = 0.97, $CHCl_3$).

<u>*Note:*</u> Alternative procedure for preparation of alkyne **14** using Dess-Martin oxidation.

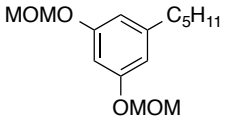
$NaHCO_3$ (210 mg, 2.5 mmol, 2.5 equiv) was added to a solution of alcohol **17** (272.5 mg, 1 mmol, 1 equiv) in 5 mL of HPLC grade CH_2Cl_2 under argon atmosphere. The suspension was cooled down to 0 °C. DMP (466 mg, 1.1 mmol, 1.1 equiv) was added to the reaction mixture in 3 portions. After stirring at 25 °C for 3 hours Florisil was added (≈4 g) and all volatiles were removed under reduced pressure. The residue was filtered through a pad of silica gel eluting with CH_2Cl_2 to give aldehyde **18** as colourless oil, which was directly used the following step.

Dimethyl (1-diazo-2oxopropyl)phosphonate (192 mg, 1.0 mmol, 1.0 equiv) and K_2CO_3 (166 mg, 1.2 mmol, 1.2 equiv) were added to a solution of aldehyde **18** in dry methanol (5 mL) under argon atmosphere and at 0 °C. The reaction mixture was stirred for 5 h at

25 °C. Then the solvent was evaporated under reduced pressure and extractive work up (CH_2Cl_2 / water) was performed. Combined organic phases were washed with brine, dried over Na_2SO_4 and purified by column chromatography (cyclohexane / EtOAc, 20 : 1) to give alkyne (207 mg, 0.78 mmol, 78% over 2 steps) as colourless oil.

Dimethyl (1-diazo-2-oxopropyl)phosphonate was synthesized according to previously reported procedure.[38]

1,3-Bis(methoxymethoxy)-5-pentylbenzene (S1)

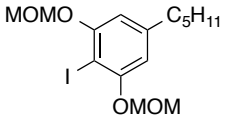


NaH (1.25 g, 31.2 mmol, 2.5 equiv.) was added to a solution of olivetol (2.25 g, 12.5 mmol, 1 equiv.) in DMF (60 mL) at 0 ºC under argon atmosphere. After 30 min methoxymethylchloride (2.37 mL, 31.2 mmol, 2.5 equiv.) was added and the reaction mixture was stirred overnight. After extractive work-up (H_2O / Et_2O), the residue was purified by column chromatography (cyclohexane / EtOAc, 9 : 1) to yield **S1** (3.25 g, 12.13 mmol, 97%) as a colourless oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.60 (t, *J* = 2.2 Hz, 1H), 6.56 (d, *J* = 2.3 Hz, 2H), 5.17 (s, 4H), 3.51 (s, 6H), 2.63 - 2.50 (m, 2H), 1.67 − 1.55 (m, 2H), 1.42 − 1.31 (m, 4H), 0.92 (t, *J* = 7.0 Hz, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 158.3, 145.7, 110.0, 102.3, 94.7, 56.2, 36.3, 31.7, 31.1, 22.7, 14.2. **HRMS-ESI** *m/z* calcd for $C_{15}H_{24}O_4Na$ $[M+Na]^+$ 291.1567, found 291.1556.

^{1}H NMR data were in accordance with those previously reported.[39]

2-Iodo-1,3-bis(methoxymethoxy)-5-pentylbenzene (23)

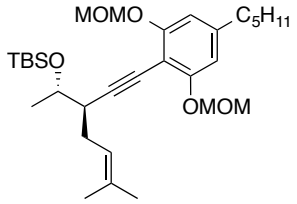


n-BuLi (5.8 mL, 14.5 mmol, 2.5 M in hexanes, 1.2 equiv) was added to a solution of 1,3-bis(methoxymethoxy)-5-pentylbenzene **S1** (3.25 g, 12.1 mmol, 1 mmol) in THF (50 mL) 0 ºC under argon atmosphere and stirred for 15 min. Then, I_2 (3.7 g, 14.5 mmol, 1.2 equiv) was added as a solution in THF (5 mL) and the reaction mixture was stirred for 2 h. MeOH (15 mL) was added and the crude was concentrated. After extractive work-up (H_2O / EtOAc), the organic layer was washed with saturated $Na_2S_2O_3$ (20 mL) and brine (20 mL), dried with Na_2SO_4 and evaporated. The residue was purified by column chromatography (cyclohexane / EtOAc, 9 : 1) to yield **23** (3.91 g, 9.92 mmol, 82%) as a yellow oil.

(38) Quesada, E.; Raw, S. A.; Reid, M.; Roman, E.; Taylor R. J. K. *Tetrahedron* **2006**, *62*, 6673−6680.
(39) Huffman, J. W.; Zhang, X.; Wu, M. J.; Joyner, H. H.; Pennington W. T. *J. Org. Chem*., **1991**, *56,* 1481−1489.

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.60 (s, 2H), 5.23 (s, 4H), 3.52 (s, 6H), 2.62 – 2.47 (m, 2H), 1.61 − 1.58 (m, 2H), 1.34 − 1.31 (m, 4H), 0.89 (t, *J* = 7.0 Hz, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 157.3, 145.7, 109.1, 95.2, 56.6, 36.3, 31.7, 31.2, 22.7, 14.2. **HRMS-ESI** *m/z* calcd for $C_{15}H_{23}O_4NaI$ $[M+Na]^+$ 417.0539, found 417.0536.

(((2*S*,3*R*)-3-((2,6-Bis(methoxymethoxy)-4-pentylphenyl)ethynyl)-6-methylhept-5-en-2-yl)oxy)*tert*-butyldimethylsilane (24)

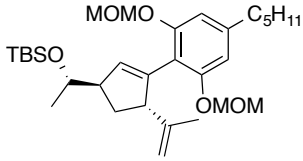


$[Pd(PPh_3)_2Cl_2]$ (174 mg, 0.25 mmol, 0.05 equiv) was added to a solution of 2-iodo-1,3-bis(methoxymethoxy)-5-pentylbenzene **23** (1.95 g, 5.0 mmol, 1 equiv) in a mixture of degassed (freeze-pump 3 cycles) Et_3N and $^iPr_2NH$ (1 : 1, 20 mL) was added at 25 ºC under argon atmosphere and stirred for 15 min, CuI (94 mg, 0.50 mmol, 0.1 equiv) and stirred for 15 min and finally enyne **14** (1.52 g, 5.7 mmol, 1.15 equiv) in solution (10 mL) drop wise. The mixture was stirred at room temperature for 16 h. The reaction was treated with saturated solution of NH_4Cl (20 mL) and extracted with CH_2Cl_2 (3 × 30 mL). The combined organic phases were washed with brine (40 mL), dried over Na_2SO_4 and purified by column chromatography (pentane to pentane / ether, 95 : 5) to give enyne **24** (2.2 g, 4.15 mmol, 83%) as a pale yellow oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.61 (s, 2H), 5.46 − 5.41 (m, 1H), 5.23 (s, 4H), 4.09 (qd, *J* = 6.2, 4.0 Hz, 1H), 3.53 (s, 6H), 2.71 (dt, *J* = 10.2, 4.2 Hz, 1H), 2.58 − 2.53 (m, 2H), 2.47 (ddd, *J* = 12.8, 7.4, 4.5 Hz, 1H), 2.27 − 2.20 (m, 1H), 1.74 (d, *J* = 0.8 Hz, 3H), 1.67 (s, 3H), 1.65 − 1.55 (m, 2H), 1.40 − 1.32 (m, 4H), 1.33 (d, *J* = 6.2 Hz, 3H), 0.95 − 0.88 (m, 9H + 3H), 0.10 (s, 3H), 0.09 (s, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 158.9, 144.5, 132.3, 123.1, 109.7, 103.4, 99.1, 95.2, 75.0, 70.1, 56.3, 41.7, 36.6, 31.7, 31.0, 27.9, 26.0, 26.0, 22.7, 19.9, 18.2, 18.0, 14.2, -4.3, -4.7. **HRMS-ESI** *m/z* calcd for $C_{31}H_{52}O_5NaSi$ $[M+Na]^+$ 555.3482, found 555.3483. $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{23}}$ = −55.9º (c = 1.01, $CHCl_3$).

<u>*Note:*</u> the reaction preferentially should be set up in glovebox.

((*S*)-1-((1*R*,4*S*)-3-(2,6-bis(methoxymethoxy)-4-pentylphenyl)-4-(prop-1-en-2-yl)cyclopent-2-en-1-yl)ethoxy)(*tert*-butyl)dimethylsilane (27)

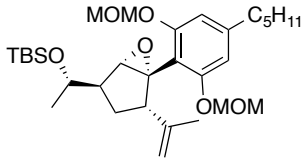


[JohnPhosAu(NCMe)]SbF_6 (152 mg, 0.20 mmol, 0.05 equiv) was added to a solution of enyne **24** (2.1 g, 3.94 mmol, 1 equiv) in DMSO (7 mL, 0.5 M) at 25 ºC under argon atmosphere and stirred for 3 h. The reaction mixture was treated with brine and

extracted with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography (cyclohexane / EtOAc, 50 : 1) to give cyclopentene **27** (1.85 g, 3.47 mmol, 88%) as a yellow oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.62 (s, 2H), 5.87 (t, J = 1.9 Hz, 1H), 5.11 (s, 4H), 4.63 (d, J = 2.6 Hz, 1H), 4.50 (dd, J = 2.6, 1.4 Hz, 1H), 4.04 − 3.97 (m, 1H), 3.75 − 3.66 (m, 1H), 3.46 (s, 6H), 3.03 − 2.93 (m, 1H), 2.59 − 2.45 (m, 2H), 1.93 (ddd, J = 13.1, 9.0, 6.6 Hz, 1H), 1.87 (ddd, J = 12.9, 8.3, 4.3 Hz, 1H), 1.64 (s, 3H), 1.62 − 1.55 (m, 2H), 1.39 − 1.26 (m, 4H), 1.17 (d, J = 6.0 Hz, 3H), 0.90 (s, 12H), 0.06 (s, 3H), 0.04 (s, 3H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ 155.8, 148.5, 143.4, 138.6, 134.5, 115.2, 110.0, 108.6, 94.9, 72.5, 56.0, 55.5, 53.3, 36.5, 32.6, 31.9, 31.1, 26.1, 22.7, 21.6, 19.3, 18.3, 14.2, − 4.1, − 4.5. **HRMS-ESI** *m/z* calcd for $C_{31}H_{52}O_5NaSi$ $[M+Na]^+$ 555.3482, found 555.3459. $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{24}}$ = +110.4º (c = 0.99, $CHCl_3$).

((*S*)-1-((1*S*,2*R*,4*S*,5*S*)-5-(2,6-bis(methoxymethoxy)-4-pentylphenyl)-4-(prop-1-en-2-yl)-6-oxabicyclo[3.1.0]hexan-2-yl)ethoxy)(*tert*-butyl)dimethylsilane (35)

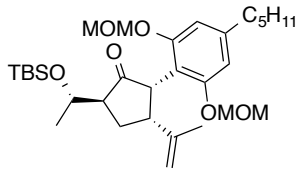


$NaHCO_3$ (583 mg, 6.94 mmol, 2 equiv) and *m*-CPBA (689 mg, 3.99 mmol, 1,15 equiv) were added to a solution of cyclopentene **27** (1.85 g, 3.47 mmol, 1 equiv) in CH_2Cl_2 (50 mL) at 0 ºC. The mixture was stirred for 3 h, allowing the ice bath to slowly warm up to at 25 ºC. The reaction mixture was diluted with CH_2Cl_2 (10 mL), and then washed with aqueous saturated $NaHCO_3$ (2 × 20 mL), followed by brine (30 mL). The organic phase was dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography (pentane / ether, 95 : 5) to give epoxide **35** (1.1 g, 1.98 mmol, 57%) as a pale yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.66 (s, 1H), 6.59 (s, 1H), 5.35 − 5.02 (m, 4H), 4.69 (bs, 1H), 4.54 (s, 1H), 4.08 (s, 1H), 3.86 (dq, J = 9.5, 6.1 Hz, 1H), 3.56 (m, 3H + 1H), 3.46 (s, 3H), 2.58 − 2.49 (m, 2H), 2.43 (q, J = 10.0 Hz, 1H), 1.62 (s, 3H), 1.61 − 1.54 (m, 2H), 1.54 − 1.48 (m, 1H), 1.47 − 1.40 (m, 1H), 1.37 − 1.30 (m, 4H), 1.19 (d, J = 6.1 Hz, 3H), 0.92 (s, 9H+3H), 0.12 (s, 3H), 0.11 (s, 3H) ppm; **^{13}C NMR** (101 MHz, $CDCl_3$) δ 158.8, 156.0, 146.5, 145.6, 111.8, 111.3, 108.2, 107.6, 94.7, 94.6, 69.9, 66.3, 65.4, 56.3, 56.2, 50.4, 49.5, 36.7, 31.8, 31.1, 29.8, 26.0, 22.9, 22.7, 21.0, 18.21, 14.2, −4.1, −4.6.

HRMS-ESI *m/z* calcd for $C_{31}H_{53}O_6Si$ $[M+H]^+$ 549.3606, found 549.3601. $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{24}}$ = −27.1º (c = 0.95, $CHCl_3$).

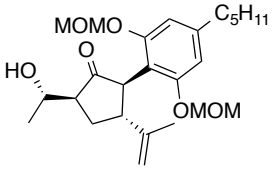
(2*S*,3*R*,5*S*)-2-(2,6-bis(methoxymethoxy)-4-pentylphenyl)-5-((*S*)-1-((*tert*-butyldimethylsilyl)oxy)ethyl)-3-(prop-1-en-2-yl)cyclopentan-1-one (36)



$BF_3{\cdot}Et_2O$ (0.49 mL, 3.94 mmol, 2 equiv) was added to a solution of **35** (1.1 g, 1.97 mmol, 1 equiv) in THF (25 mL) at 25 ºC and the mixture was stirred for 30 min. Saturated $NaHCO_3$ solution (15 mL) was added and stirred for 15 min. The reaction mixture was diluted and extracted with EtOAc (2 × 20 mL) and the organic phase washed with brine (25 mL). The organic phase was then dried over Na_2SO_4 and concentrated. Purification was made by column chromatography (pentane / ether, 9 : 1) giving the titled product as pale yellow oil (1 g, 1.83 mmol, 92%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.65 (bs, 2H), 5.20 − 5.03 (m, 4H), 4.76 (bs, 1H), 4.69 (bs, 1H), 4.45 (qd, *J* = 6.3, 4.6 Hz, 1H), 4.13 (dd, *J* = 12.2, 1.7 Hz, 1H), 3.51 − 3.35 (bs, 6H), 3.29 (ddd, *J* = 12.2, 10.4, 7.7 Hz, 1H), 2.86 (dtd, *J* = 10.8, 4.4, 1.7 Hz, 1H), 2.60 − 2.52 (m, 2H), 2.38 (ddd, *J* = 13.7, 7.8, 4.3 Hz, 1H), 2.01 (ddd, *J* = 13.8, 11.1, 10.3 Hz, 1H), 1.78 (d, *J* = 0.7 Hz, 3H), 1.65 −1.58 (m, 2H), 1.40 − 1.30 (m, 4H), 1.22 (d, *J* = 6.3 Hz, 3H), 0.92 (bs, 9H + 3H), 0.11 (s, 3H), 0.10 (s, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 215.0, 146.7, 144.0, 112.1, 110.8, 108.2, 95.2, 93.8, 67.9, 56.2, 55.9, 53.7, 51.6, 47.5, 36.6, 31.9, 31.1, 26.6, 26.0, 22.7, 19.6, 19.4, 18.2, 14.2, −4.4, −4.7. **HRMS-ESI** *m/z* calcd for $C_{31}H_{52}NaO_6Si$ $[M+Na]^+$ 571.3425, found 571.3416. $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{23}}$ = +4.1º (c = 1.09, $CHCl_3$).

(2*R*,3*R*,5*S*)-2-(2,6-bis(methoxymethoxy)-4-pentylphenyl)-5-((*S*)-1-hydroxyethyl)-3-(prop-1-en-2-yl)cyclopentan-1-one (37)



HCl 10% (8 mL) was added to a solution of **36** (1 g, 1.82 mmol) in THF (16 mL) at 25 ºC and the mixture was stirred for 1 h. $NaHCO_3$ was added to neutralize the solution. After extractive work-up (EtOAc), the organic layer was washed with brine (15 mL), dried with Na_2SO_4 and evaporated. The residue was purified by column chromatography (cyclohexane / EtOAc, 7 : 3) to yield ketone **37** (690 mg, 87%) as a yellow oil.

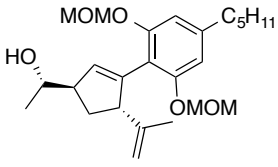
The same product was obtained from epoxide **38** (12.5 mg, 0.03 mmol, 1 equiv) and $BF_3{\cdot}Et_2O$ (7 mL, 0.06 mmol, 2 equiv) following the procedure previously described to obtain ketone **36** (6 mg, 48%).

Alternative procedures for the synthesis of ketone **36**:

ZnI_2 (22 mg, 0.07 mmol, 2 equiv) and $NaBH_4$ (6.5 g, 0.17 mmol, 5 equiv) were added to a solution of **38** (15 mg, 0.03 mmol, 1 equiv) in dichloroethane (5 mL) at 25 ºC and the mixture was stirred for 14 h. The crude was filtrated to remove the remaining salts, the solvent was evaporated and the residue was purified by column chromatography (cyclohexane / EtOAc 8 : 2) to yield ketone **36** (9.5 mg, 63%). *Note:* Same product was obtained in absence of $NaBH_4$, however lower yields and more decomposition products were obtained.

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.63 (s, 2H), 5.16 − 5.03 (m, 4H), 4.74 (bs, 1H), 4.70 (pt, *J* = 1.6 Hz, 1H), 4.09 (s, 1H), 4.03 (dd, *J* = 10.9, 1.8 Hz, 1H), 4.03 − 3.95 (m, 1H), 3.42 (s, 6H), 3.19 (td, *J* = 10.5, 7.5 Hz, 1H), 2.55 − 2.48 (m, 2H), 2.38 (tdd, *J* = 9.7, 3.8, 1.6 Hz, 1H), 2.13 (dt, *J* = 13.5, 9.9 Hz, 1H), 1.99 (ddd, *J* = 13.5, 7.5, 3.9 Hz, 1H), 1.76 (s, 3H), 1.62 − 1.54 (m, 2H), 1.35 − 1.31 (m, 4H), 1.30 (d, *J* = 6.5 Hz, 3H), 0.92 − 0.85 (m, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 221.3, 145.9, 144.3, 113.1, 111.3, 108.1, 95.1, 94.4, 68.7, 56.3, 53.9, 50.9, 47.9, 36.6, 31.8, 31.1, 30.2, 22.7, 22.1, 19.6, 14.2. **HRMS-ESI** *m/z* calcd for $C_{25}H_{38}NaO_6$ $[M+Na]^+$ 457.2561, found 457.2547. $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{24}}$ = −18.6º (c = 0.90, $CHCl_3$).

(*S*)-1-((1*R*,4*S*)-3-(2,6-bis(methoxymethoxy)-4-pentylphenyl)-4-(prop-1-en-2-yl)cyclopent-2-en-1-yl)ethan-1-ol (S2)

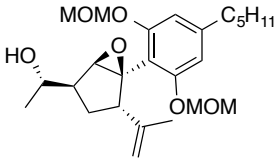


TBAF (0.31 mL, 1 M in THF, 1.1 equiv) was added to a solution of cyclopentene **27** (150 mg, 0.28 mmol, 1 equiv) in THF (2 mL). The reaction mixture was stirred at 25 ºC for 14 h. The solvent was evaporated and the residue was purified by column chromatography (cyclohexane / EtOAc 8 : 2) to give alcohol **S2** (98 mg, 0.23 mmol, 83%) as a colorless oil.

^{1}H NMR (300 MHz, $CDCl_3$) δ 6.62 (s, 2H), 5.82 (t, *J* = 2.1 Hz, 1H), 5.11 (s, 4H), 4.65 - 4.61 (m, 1H), 4.57 − 4.49 (m, 1H), 4.11 − 3.98 (m, 1H), 3.75 (q, *J* = 6.1 Hz, 1H), 3.45 (s, 6H), 3.06 − 2.93 (m, 1H), 2.58 − 2.45 (m, 2H), 2.08 − 1.95 (m, 1H), 1.86 (d, *J* = 6.5 Hz, 1H), 1.62 (s, 3H), 1.60 − 1.51 (m, 2H), 1.41 − 1.29 (m, 4H), 1.20 (d, *J* = 6.3 Hz,

3H), 0.90 (t, *J* = 6.4 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 155.5, 147.9, 143.8, 142.3, 131.1, 114.6, 110.7, 108.3, 94.8, 71.8, 56.1, 55.7, 52.7, 36.5, 33.5, 31.8, 31.1, 22.6, 22.0, 19.1, 14.2. **HRMS-ESI** *m/z* calcd for $C_{25}H_{38}O_5Na$ $[M+Na]^+$ 441.2617, found 441.2608. $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{27}}$ = +116.1º (c = 1.02, $CHCl_3$).

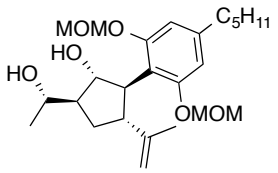
(*S*)-1-((1*R*,2*S*,4*S*,5*R*)-5-(2,6-bis(methoxymethoxy)-4-pentylphenyl)-4-(prop-1-en-2-yl)-6-oxabicyclo[3.1.0]hexan-2-yl)ethan-1-ol (38)



$NaHCO_3$ (19 mg, 0.22 mmol, 2 equiv) and *m*-CPBA (22 mg, 0.13 mmol, 1.15 equiv) were added to a solution of cyclopentene **S2** (46 mg, 0.11 mmol, 1 equiv) in CH_2Cl_2 (2 mL) at 0 ºC in an open flask. The mixture was stirred for 4 h, allowing the ice bath to slowly warm up to 25 ºC. The reaction mixture was diluted with CH_2Cl_2 (10 mL), and then washed with aqueous saturated $NaHCO_3$ (2 × 10 mL), followed by brine (10 mL). The organic phase was dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography (cyclohexane / EtOAc 6 : 4) to give epoxide **38** (28 mg, 0.064 mmol, 58%) as a colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.66 (s, 1H), 6.60 (s, 1H), 5.35 − 5.22 (m, 2H), 5.17 − 5.08 (m, 2H), 4.70 (dd, *J* = 1.5, 0.7 Hz, 1H), 4.57 (t, *J* = 1.8 Hz, 1H), 4.10 (d, *J* = 1.3 Hz, 1H), 3.98 − 3.88 (m, 1H), 3.57 − 3.53 (m, 3H + 1H), 3.47 (s, 3H), 2.59 − 2.50 (m, 2H), 2.43 (q, *J* = 9.1, 8.6 Hz, 1H), 1.63 (s, 3H), 1.61 − 1.54 (m, 4H), 1.39 − 1.31 (m, 4H), 1.29 (d, *J* = 6.3 Hz, 3H), 0.90 (t, *J* = 6.9 Hz, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 158.7, 156.0, 146.2, 145.7, 112.0, 111.2, 108.3, 107.8, 94.8, 94.7, 69.3, 65.5, 65.4, 56.3, 50.2, 48.3, 36.6, 31.7, 31.0, 30.5, 29.9, 22.7, 22.6, 21.1, 14.2. **HRMS-ESI** *m/z* calcd for $C_{25}H_{38}NaO_6$ $[M+Na]^+$ 457.2561, found 457.2567. $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{25}}$ = −11.6º (c = 1.07, $CHCl_3$).

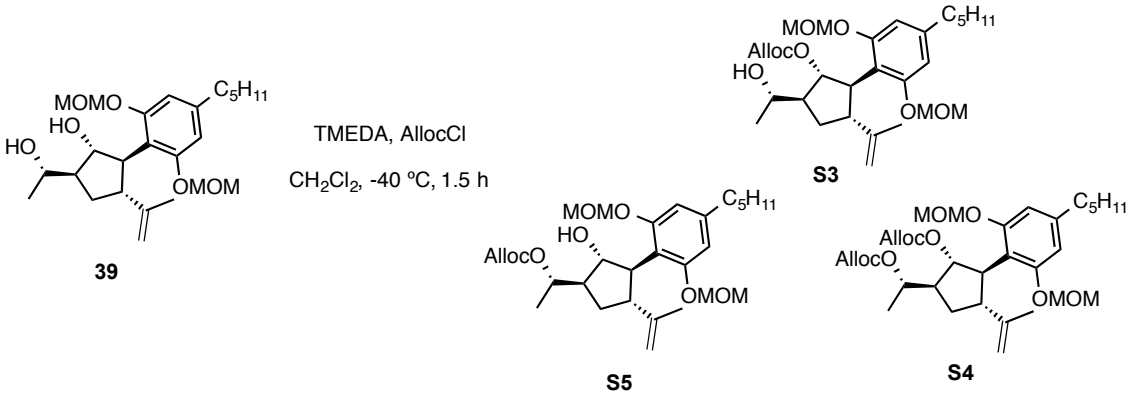
(1*R*,2*R*,3*R*,5*S*)-2-(2,6-bis(methoxymethoxy)-4-pentylphenyl)-5-((*S*)-1-hydroxyethyl)-3-(prop-1-en-2-yl)cyclopentan-1-ol (40)



Sodium triacetoxyborohydride (258 mg, 1.22 mmol, 1.1 equiv) was added to a solution of **37** (480 mg, 1.11 mmol, 1 equiv) in CH_2Cl_2 (37 mL, 0.03 M) at 25 ºC and mixture was stirred for 48 h. $NaHCO_3$ (20 mL) was added to the solution. After extractive work-up (CH_2Cl_2), the organic layer was dried with Na_2SO_4 and evaporated. The residue was purified by column chromatography (cyclohexane / EtOAc, 8 : 2 to 6 : 4) to yield diol **37** (230 mg, 48%, 77% brsm) as a colorless oil. 180 mg of the hydroxyketone **37** was recovered.

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.60 (s, 2H), 5.16 (s, 4H), 4.68 − 4.63 (m, 1H), 4.58 (dd, *J* = 2.1, 1.3 Hz, 1H), 4.53 (dd, *J* = 9.7, 8.7 Hz, 2H), 3.85 − 3.74 (m, 1H), 3.67 (t, *J* = 9.8 Hz, 1H), 3.48 (s, 6H), 3.16 (td, *J* = 10.1, 5.2 Hz, 1H), 2.60 - 2.45 (m, 2H), 1.89 (p, *J* = 9.0 Hz, 1H), 1.79 (ddd, *J* = 14.5, 9.2, 5.4 Hz, 1H), 1.71 (s, 3H), 1.64 (dt, *J* = 13.3, 10.2 Hz, 1H), 1.61 − 1.54 (m, 2H), 1.36 − 1.29 (m, 4H), 1.21 (d, *J* = 6.1 Hz, 3H), 0.93 − 0.85 (m, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 156.9, 148.2, 143.4, 115.8, 109.5, 109.1, 95.2, 80.9, 73.7, 56.4, 52.5, 47.9, 45.6, 36.4, 31.8, 31.1, 30.4, 22.7, 22.4, 20.1, 14.2. **HRMS-ESI** *m/z* calcd for $C_{25}H_{40}NaO_6$ $[M+Na]^+$ 459.2717, found 459.2707. $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{24}}$ = −26.1º (c = 1.09, $CHCl_3$).

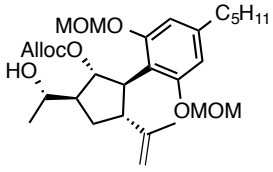
Alloc protection of diol 39



TMEDA (37 mL, 0.25 mmol, 1.2 equiv) was added to the solution of diol **39** (90 mg, 0.21 mmol, 1 equiv) in CH_2Cl_2 (4 mL) at −40 ºC. Then, allyl chloroformate (23 mL, 0.22 mmol, 1.05 equiv) in CH_2Cl_2 (1 mL) was added dropwise and the solution was stirred at −40 ºC for 1.5 h. The solvent was evaporated and the residue was purified by column chromatography (cyclohexane / EtOAc 8 : 2 to 6 : 4) to obtain monocarbonate **S3** (44 mg, 41%, 72% brsm), dicarbonate **S4** (20 mg), monocarbonate **S5** (11 mg) and diol **39** (30 mg).

Protected alcohol **S4** and **S5** were hydrolyzed with K_2CO_3 in methanol to recover 20 mg of diol **39** (92% brsm for **S3**).

Allyl ((1*R*,2*R*,3*R*,5*S*)-2-(2,6-bis(methoxymethoxy)-4-pentylphenyl)-5-((*S*)-1-hydroxyethyl)-3-(prop-1-en-2-yl)cyclopentyl) carbonate (S3)

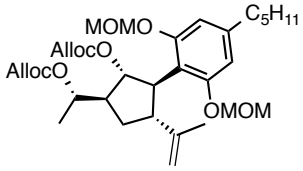


Colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.60 (s, 2H), 5.82 (ddt, *J* = 17.2, 10.4, 5.8 Hz, 1H), 5.57 (dd, *J* = 7.8, 3.6 Hz, 1H), 5.32 − 5.12 (m,

4H + 2H), 4.61 (bs, 1H), 4.58 (bs, 1H), 4.56 − 4.42 (m, 2H), 4.04 − 3.80 (m, 2H), 3.49 (s, 6H), 3.19 (td, *J* = 11.3, 6.9 Hz, 1H), 2.56 − 2.45 (m, 2H), 2.08 (tt, *J* = 9.2, 3.3 Hz, 1H), 2.00 (ddd, *J* = 13.1, 10.9, 9.4 Hz, 1H), 1.72 (ddd, *J* = 13.1, 6.9, 3.0 Hz, 1H), 1.67 (s, 3H), 1.62 − 1.54 (m, 2H), 1.35 – 1.28 (m, 4H), 1.26 (d, *J* = 6.1 Hz, 3H), 0.89 (t, *J* = 6.8 Hz, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 156.3, 155.9, 145.9, 143.5, 131.6, 118.9, 114.5, 111.0, 108.1, 94.6, 85.7, 69.4, 68.5, 56.3, 53.2, 47.8, 45.8, 36.5, 33.0, 31.9, 31.1, 22.7, 22.4, 19.5, 14.2. **HRMS-ESI** *m/z* calcd for $C_{29}H_{44}NaO_8$ $[M+Na]^+$ 543.2928, found 543.2934. $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{28}}$ = +12.6º (c = 1.04, $CHCl_3$).

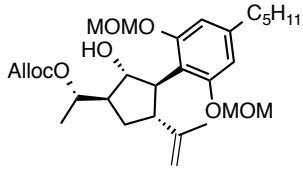
Allyl ((*S*)-1-((1*S*,2*R*,3*R*,4*R*)-2-(((allyloxy)carbonyl)oxy)-3-(2,6-bis(methoxymethoxy)-4-pentylphenyl)-4-(prop-1-en-2-yl)cyclopentyl)ethyl) carbonate (S4)



Colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.59 (bs, 2H), 5.92 (ddt, *J* = 17.3, 10.5, 5.7 Hz, 1H), 5.80 − 5.68 (m, 2H), 5.34 (dq, *J* = 17.2, 1.5 Hz, 1H), 5.28 – 5.04 (m, 3H+2H+2H), 4.95 (p, *J* = 6.4 Hz, 1H), 4.65 (bs, 1H), 4.60 (dq, *J* = 5.8, 1.6 Hz, 2H), 4.59 (bs, 1H), 4.47 − 4.34 (m, 2H), 3.87 (dd, *J* = 11.2, 9.3 Hz, 1H), 3.49 (s, 6H), 3.26 (dt, *J* = 11.3, 8.7 Hz, 1H), 2.54 − 2.47 (m, 2H), 2.45 (dt, *J* = 10.4, 6.6 Hz, 1H), 1.96 (ddd, *J* = 13.5, 10.4, 8.9 Hz, 1H), 1.80 (ddd, *J* = 13.4, 8.6, 6.1 Hz, 1H), 1.67 (s, 3H), 1.61 − 1.54 (m, 2H), 1.35 (d, *J* = 6.3 Hz, 3H), 1.34 − 1.27 (m, 4H), 1.25 (s, 3H), 0.88 (t, *J* = 6.9 Hz, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 154.9, 154.5, 146.5, 143.4, 132.0, 131.9, 118.7, 118.2, 113.9, 110.5, 108.2, 94.9, 82.7, 76.9, 68.3, 68.1, 56.2, 47.7, 46.5, 45.6, 36.5, 31.8, 31.0, 31.0, 29.8, 22.7, 19.7, 17.9, 14.2. **HRMS-ESI** *m/z* calcd for $C_{33}H_{48}NaO_{10}$ $[M+Na]^+$ 627.3140, found 627.3155. $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{27}}$ = −11.2º (c = 1.10, $CHCl_3$).

Allyl ((*S*)-1-((1*R*,2*R*,3*R*,4*R*)-3-(2,6-bis(methoxymethoxy)-4-pentylphenyl)-2-hydroxy-4-(prop-1-en-2-yl)cyclopentyl)ethyl) carbonate (S5)

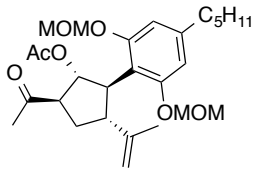


Colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.63 (s, 2H), 5.94 (ddt, *J* = 17.1, 10.4, 5.8 Hz, 1H), 5.36 (dd, *J* = 17.2, 1.5 Hz, 1H), 5.27 (dd, *J* = 10.4, 1.3 Hz, 1H), 5.19 (s, 4H), 4.97 − 4.88 (m, 1H), 4.67 (bs, 1H), 4.65 − 4.62 (m, 2H), 4.62 − 4.58 (m, 2H), 3.69 (dd, *J* = 11.0, 9.3 Hz, 1H), 3.50 (s, 6H), 3.30 (dt, *J* = 10.9, 8.6 Hz, 1H), 2.58 − 2.48 (m, 2H), 2.22 (dq, *J* = 10.2, 7.0 Hz, 1H), 1.95 (ddd, *J* =

13.4, 10.2, 8.3 Hz, 1H), 1.76 (ddd, *J* = 13.3, 8.9, 6.8 Hz, 1H), 1.70 (s, 3H), 1.64 − 1.56 (m, 2H), 1.39 (d, *J* = 6.3 Hz, 3H), 1.37 − 1.31 (m, 4H), 0.92 (t, *J* = 7.0 Hz, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 156.9, 155.0, 147.4, 143.3, 131.9, 118.8, 115.5, 109.9, 108.8, 94.9, 78.4, 68.3, 56.3, 50.4, 48.6, 46.2, 36.4, 31.9, 31.4, 31.1, 22.7, 20.0, 18.6, 14.2. **HRMS-ESI** *m/z* calcd for $C_{29}H_{44}NaO_8$ $[M+Na]^+$ 543.2928, found 543.2933. $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{28}}$ = −13.4º (c = 0.83, $CHCl_3$).

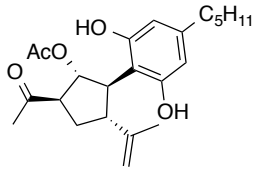
(1*R*,2*R*,3*R*,5*R*)-5-acetyl-2-(2,6-bis(methoxymethoxy)-4-pentylphenyl)-3-(prop-1-en-2-yl)cyclopentyl allyl carbonate (40)



$NaHCO_3$ (14 mg, 0.17 mmol, 2 equiv) and Dess-Martin periodinane (70 mg, 0.17 mmol, 2 equiv) were added to a stirred solution of alcohol **S3** (43 mg, 0.08 mmol, 1 equiv) in CH_2Cl_2 (2 mL) at 25 ºC and the mixture was stirred for 1.5 h. Saturated $NaHCO_3$ solution (10 mL) was added. After extractive work-up (CH_2Cl_2), the organic layer was dried with Na_2SO_4 and evaporated. The residue was purified by column chromatography (cyclohexane / EtOAc 8 : 2) to yield ketone **40** (37 mg, 87%) as colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.60 (bs, 2H), 5.82 (ddt, *J* = 17.2, 10.4, 5.8 Hz, 1H), 5.75 (dd, *J* = 7.6, 4.2 Hz, 1H), 5.30 − 5.16 (m, 2H), 5.18 − 5.09 (m, 4H), 4.64 (bs, 1H), 4.62 − 4.58 (m, 1H), 4.53 − 4.46 (m, 2H), 3.87 (dd, *J* = 11.6, 7.6 Hz, 1H), 3.52 − 3.45 (m, 6H), 3.25 (td, *J* = 11.2, 7.1 Hz, 1H), 3.09 (dt, *J* = 9.6, 3.8 Hz, 1H), 2.57 − 2.45 (m, 2H), 2.32 (s, 3H), 2.17 (ddd, *J* = 12.8, 7.1, 3.4 Hz, 1H), 1.96 (ddd, *J* = 12.8, 10.9, 9.6 Hz, 1H), 1.66 (s, 3H), 1.62 – 1.53 (m, 2H), 1.37 − 1.27 (m, 4H), 0.89 (t, *J* = 7.0 Hz, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 207.8, 156.3, 154.8, 145.6, 143.6, 131.7, 118.9, 114.3, 111.1, 108.2, 94.7, 84.4, 68.4, 57.2, 56.2, 48.0, 45.8, 36.5, 31.9, 31.7, 31.0, 29.0, 22.7, 19.7, 14.2. **HRMS-ESI** *m/z* calcd for $C_{29}H_{42}NaO_8$ $[M+Na]^+$ 541.2772, found 541.2768. $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{26}}$ = −14.6º (c = 1.02, $CHCl_3$).

(1*R*,2*R*,3*R*,5*R*)-5-acetyl-2-(2,6-dihydroxy-4-pentylphenyl)-3-(prop-1-en-2-yl)cyclopentyl allyl carbonate (S6)

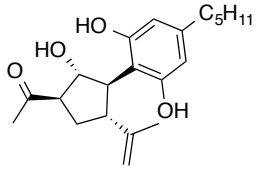


$MgBr_2$ (124 mg, 0.68 mmol, 10 equiv) and BnSH (79 mL, 0.68 mmol, 10 equiv) were added to a solution of ketone **40** (35 mg, 0.07 mmol, 1 equiv) in Et_2O (1.5 mL) in an open flask, and stirred for 30 h at 25 ºC. The crude was filtrated to remove the salts and the residue was

purified by column chromatography (cyclohexane / EtOAc 8 : 2) to yield ketone **S6** (18 mg, 62%) as a colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.19 (s, 2H), 5.86 (ddt, *J* = 17.2, 10.4, 5.8 Hz, 1H), 5.61 (dd, *J* = 7.5, 3.4 Hz, 1H), 5.30 (dq, *J* = 17.2, 1.5 Hz, 1H), 5.22 (dq, *J* = 10.4, 1.2 Hz, 1H), 4.72 (bs, 1H), 4.65 (bs, 1H), 4.59 − 4.48 (m, 2H), 3.81 (dd, *J* = 12.1, 7.5 Hz, 1H), 3.27 − 3.20 (m, 1H), 3.17 (dt, *J* = 7.5, 3.7 Hz, 1H), 2.45 − 2.39 (m, 2H), 2.34 (s, 3H), 2.11 − 2.05 (m, 2H), 1.68 (s, 3H), 1.57 − 1.50 (m, 2H), 1.34 − 1.27 (m, 4H), 0.88 (t, *J* = 7.0 Hz, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 210.7, 155.1, 154.8, 144.9, 143.5, 131.6, 119.2, 111.7, 109.8, 84.2, 68.7, 57.0, 47.4, 45.3, 35.6, 32.4, 31.7, 30.7, 29.9, 29.0, 22.7, 19.7, 14.2. **HRMS-ESI** *m/z* calcd for $C_{25}H_{34}NaO_6$ $[M+Na]^+$ 453.2248, found 453.2247. $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{26}}$ = −0.2º (c = 1.05, $CHCl_3$).

Cannabimovone (6)

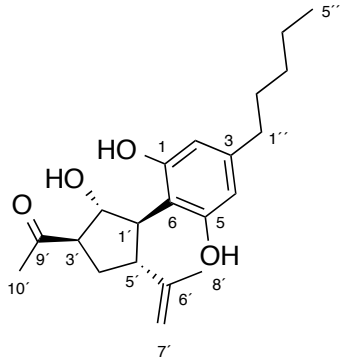


$Pd(PPh_3)_4$ (2.1 mg, 0.002 mmol, 0.05 equiv) and dimedone (10 mg, 0.07 mmol, 2 equiv) were added to a solution of ketone **S8** (16 mg, 0.04 mmol, 1 equiv) in THF (2 mL), and stirred for 1 h at 25 ºC. The solvent was evaporated and the residue was purified by column chromatography (pentane / Et_2O 3 : 7) to yield cannabimovone **6** (11 mg, 85%) as colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.19 (s, 2H), 5.66 (s, 2H), 4.76 (dd, *J* = 9.0, 6.8 Hz, 1H), 4.71 (bs, 1H), 4.63 (bs, 1H), 3.52 (dd, *J* = 11.3, 9.0 Hz, 1H), 3.33 (dt, *J* = 11.3, 8.7 Hz, 1H), 3.04 (dt, *J* = 10.4, 6.5 Hz, 1H), 2.45 − 2.37 (m, 2H), 2.27 (s, 3H), 2.12 (ddd, *J* = 13.1, 8.5, 6.2 Hz, 1H), 2.00 (ddd, *J* = 13.2, 10.4, 9.0 Hz, 1H), 1.69 (m, 3H), 1.58 − 1.51 (m, 2H), 1.34 − 1.27 (m, 4H), 0.88 (t, *J* = 6.9 Hz, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 211.9, 155.7, 146.6, 143.3, 110.4, 110.3, 109.1, 77.9, 58.2, 48.5, 45.5, 35.6, 31.7, 31.2, 30.7, 29.7, 22.7, 20.2, 14.2. **HRMS-ESI** *m/z* calcd for $C_{21}H_{30}NaO_4$ $[M+Na]^+$ 369.2036, found 369.2023. $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{28}}$ = −6.8º (c = 0.70, $CHCl_3$).

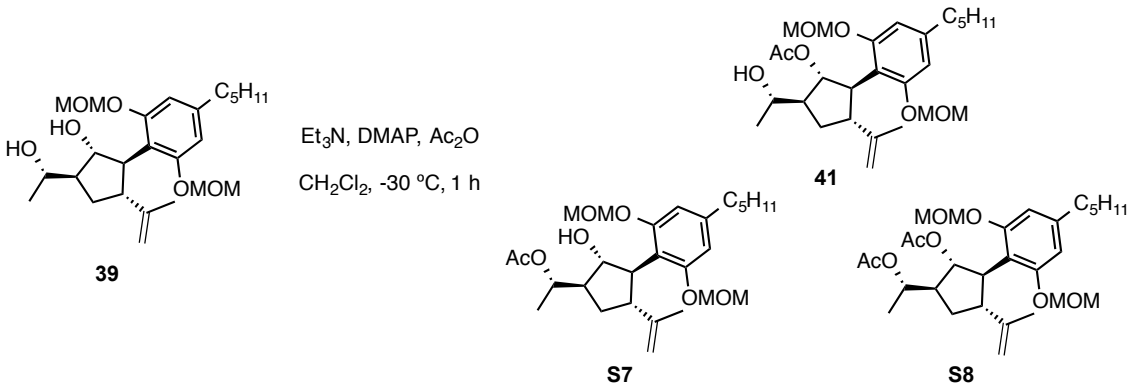
NMR data were in accordance with those previously reported.[12]

Table 12: Comparison with NMR data of isolated cannabimovone



Position	^{13}C NMR of isolated cannabimovone[12]	^{13}C NMR of our synthetic cannabimovone (d ppm)
5´´	14.3	14.2 (–0.1)
8´	20.0	20.2 (+0.2)
4´´	22.7	22.7 (0)
10´	29.5	29.7 (+0.2)
2´´	30.7	30.7 (0)
4´	31.2	31.2 (0)
3´´	31.5	31.7 (+0.2)
1´´	35.5	35.6 (+0.1)
5´	45.3	45.5(+0.2)
1´	48.4	48.5 (+0.1)
3´	58.0	58.2 (0)
2´	77.9	77.9 (0)
2/4	109.0	109.1 (0)
6	110.0	110.3 (+0.3)
7´	110.4	110.4 (0)
3	144.1	143.3 (–0.8)
6´	146.3	146.6 (+0.3)
1/5	155.4	155.7 (+0.3)
9´	211.1	211.9 (+0.8)

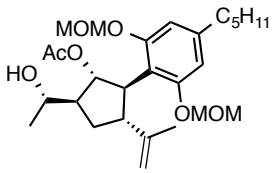
Acetylation of diol 39



Et_3N (84 mL, 0.61 mmol, 3 equiv) and DMAP (2.5 mg, 0.02 mmol, 0.1 equiv) were added to the solution of diol **39** (88 mg, 0.20 mmol, 1 equiv) in dry CH_2Cl_2 (3 mL) at −30 ºC. Then, Ac_2O (20 mL, 0.21 mmol, 1.05 equiv) in CH_2Cl_2 (1.5 mL) was added dropwise and the solution was stirred at −30 ºC for 1h. The solvent was evaporated and the residue was purified by column chromatography (cyclohexane / EtOAc 8 : 2 to 6 : 4) to obtain monoacetate **41** (48 mg, 50%, 56% brsm), diacetate **S8** (14 mg), monoacetate **S7** (24 mg) and diol **39** (10 mg).

Protected diols **S8** and **S9** were hydrolyzed with K_2CO_3 in methanol to recover 28 mg of diol **39** (88% brsm for **S7**).

(1*R*,2*R*,3*R*,5*S*)-2-(2,6-bis(methoxymethoxy)-4-pentylphenyl)-5-((*S*)-1-hydroxyethyl)-3-(prop-1-en-2-yl)cyclopentyl acetate (41)

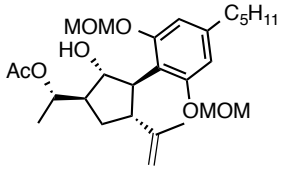


Colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.59 (s, 2H), 5.66 (dd, *J* = 7.9, 3.0 Hz, 1H), 5.17 (bs, 4H), 4.62 (bs, 1H), 4.59 (bs, 1H), 3.91 − 3.81 (m, 2H), 3.50 (s, 6H), 3.24 − 3.13 (m, 1H), 2.67 − 2.44 (m, 2H), 2.05 − 1.97 (m, 2H), 1.95 (s, 3H), 1.75 − 1.68 (m, 1H), 1.67 (s, 3H), 1.62 − 1.53 (m, 2H), 1.35 − 1.28 (m, 4H), 1.24 (d, *J* = 6.1 Hz, 3H), 0.89 (t, *J* = 6.8 Hz, 4H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 172.9, 156.3, 146.0, 143.4, 114.6, 110.9, 108.3, 94.6, 82.2, 69.6, 56.3, 53.5, 47.6, 45.9, 36.4, 33.2, 31.9, 31.0, 22.7, 22.3, 21.6, 19.6, 14.2. **HRMS-ESI** *m/z* calcd for $C_{27}H_{42}NaO_7$ $[M+Na]^+$ 501.2823, found 501.2825. $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{23}}$ = −0.9º (c = 0.95, $CHCl_3$).

Chapter 1. Synthesis of (−)-Cannabimovone and Structural Reassignment of Anhydrocannabimovone

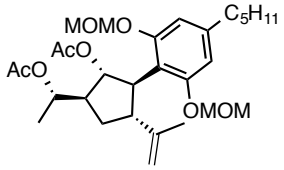
(*S*)-1-((1*R*,2*R*,3*R*,4*R*)-3-(2,6-bis(methoxymethoxy)-4-pentylphenyl)-2-hydroxy-4-(prop-1-en-2-yl)cyclopentyl)ethyl acetate (S7)



Colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.60 (s, 2H), 5.16 (s, 4H), 5.02 (dq, *J* = 8.2, 6.2 Hz, 1H), 4.65 (bs, 1H), 4.58 (bs, 1H), 4.48 (dd, *J* = 9.3, 7.3 Hz, 1H), 3.65 (dd, *J* = 10.9, 9.3 Hz, 1H), 3.48 (s, 6H), 3.25 (dt, *J* = 10.9, 8.5 Hz, 1H), 2.60 − 2.43 (m, 2H), 2.14 (dq, *J* = 9.9, 7.4 Hz, 1H), 2.04 (s, 3H), 1.97 − 1.83 (m, 1H), 1.76 − 1.69 (m, 1H), 1.68 (s, 3H), 1.63 − 1.52 (m, 2H), 1.35 − 1.31 (m, 4H), 1.30 (d, *J* = 6.2 Hz, 3H), 0.90 (t, *J* = 6.9 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 170.9, 156.8, 147.4, 143.3, 115.4, 109.9, 108.8, 95.0, 78.8, 74.2, 56.3, 50.5, 48.5, 46.0, 36.4, 31.8, 31.4, 31.1, 22.7, 21.6, 19.9, 18.9, 14.2. **HRMS-ESI** *m/z* calcd for $C_{27}H_{42}NaO_7$ $[M+Na]^+$ 501.2823, found 501.2824. $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{23}}$ = −27.3º (c = 0.96, $CHCl_3$).

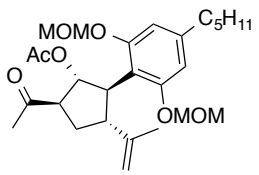
(*S*)-1-((1*S*,2*R*,3*R*,4*R*)-2-acetoxy-3-(2,6-bis(methoxymethoxy)-4-pentylphenyl)-4-(prop-1-en-2-yl)cyclopentyl)ethyl acetate (S8)



Colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.56 (bs, 2H), 5.86 (dd, *J* = 9.4, 6.8 Hz, 1H), 5.16 (bs, 4H), 5.01 (dq, *J* = 7.9, 6.3 Hz, 1H), 4.64 (bs, 1H), 4.58 (bs, 1H), 3.77 (dd, *J* = 11.4, 9.4 Hz, 1H), 3.49 (s, 6H), 3.23 (dt, *J* = 11.4, 8.8 Hz, 1H), 2.57 − 2.40 (m, 2H), 2.37 − 2.27 (m, 1H), 2.00 (s, 3H), 1.97 − 1.89 (m, 1H), 1.87 (s, 3H), 1.75 (ddd, *J* = 13.2, 8.4, 5.8 Hz, 1H), 1.67 (s, 3H), 1.61 − 1.52 (m, 2H), 1.37 − 1.28 (m, 4H), 1.27 (d, *J* = 6.3 Hz, 3H), 0.87 (t, *J* = 6.9 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 170.8, 170.1, 146.6, 143.3, 114.1, 110.5, 108.4, 94.9, 78.5, 72.8, 56.1, 47.9, 46.6, 45.8, 36.4, 31.9, 31.1, 30.9, 22.7, 21.5, 21.3, 19.7, 18.1, 14.2. **HRMS-ESI** *m/z* calcd for $C_{29}H_{44}NaO_8$ $[M+Na]^+$ 543.2928, found 543.2909. $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{22}}$ = −14.7º (c = 0.95, $CHCl_3$).

(1*R*,2*R*,3*R*,5*R*)-5-acetyl-2-(2,6-bis(methoxymethoxy)-4-pentylphenyl)-3-(prop-1-en-2-yl)cyclopentyl acetate (42)

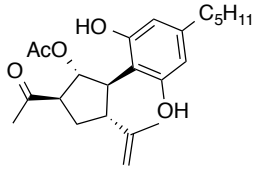


$NaHCO_3$ (17 mg, 0.20 mmol, 2 equiv) and Dess-Martin periodinane (85 mg, 0.20 mmol, 2 equiv) were added to a stirred solution of alcohol **41** (48 mg, 0.10 mmol, 1 equiv) in CH_2Cl_2 (2 mL) and the mixture was stirred for 1 h at 25 ºC. Saturated

$NaHCO_3$ solution (5 mL) was added. After extractive work-up (CH_2Cl_2), the organic layer was dried with Na_2SO_4 and evaporated. The residue was purified by column chromatography (cyclohexane / EtOAc 8 : 2) to yield ketone **42** (35 mg, 73%) as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.59 (s, 2H), 5.79 (dd, *J* = 7.8, 4.4 Hz, 1H), 5.20 − 5.09 (m, 4H), 4.65 (bs, 1H), 4.60 (bs, 1H), 3.81 (dd, *J* = 11.6, 7.8 Hz, 1H), 3.48 (s, 6H), 3.27 (td, *J* = 11.2, 7.1 Hz, 1H), 2.97 (dt, *J* = 9.6, 3.9 Hz, 1H), 2.57 − 2.42 (m, 2H), 2.31 (s, 3H), 2.21 − 2.11 (m, 1H), 1.95 (s, 3H), 1.99 − 1.87 (m, 1H), 1.66 (s, 3H), 1.62 − 1.52 (m, 2H), 1.39 − 1.25 (m, 4H), 0.96 − 0.82 (t, *J* = 7.0 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 208.3, 171.0, 156.4, 145.8, 143.5, 114.5, 110.9, 108.3, 94.5, 80.8, 57.4, 56.2, 47.8, 45.7, 36.5, 31.9, 31.9, 31.0, 28.8, 22.6, 21.3, 19.8, 14.2. **HRMS-ESI** *m/z* calcd for $C_{27}H_{40}NaO_7$ $[M+Na]^+$ 499.2666, found 499.2655. $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{25}}$ = −24.2º (c = 1.00, $CHCl_3$);

(1*R*,2*R*,3*R*,5*R*)-5-acetyl-2-(2,6-dihydroxy-4-pentylphenyl)-3-(prop-1-en-2-yl)cyclopentyl acetate (43)

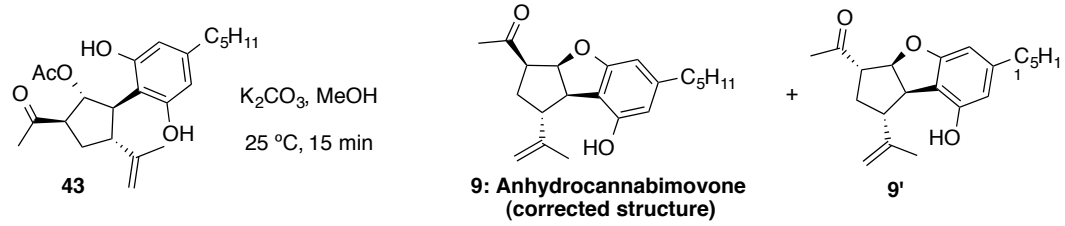


$MgBr_2$ (135 mg, 0.73 mmol, 10 equiv) and BnSH (86 mL, 0.73 mmol, 10 equiv) were added to solution of ketone **42** (35 mg, 0.07 mmol, 1 equiv) in Et_2O (1.5 mL) in an open flask, and stirred for 24 h at 25 ºC. The crude was filtrated to remove the salts and the residue was purified by column chromatography (cyclohexane / EtOAc 7 : 3) to yield ketone **43** (26 mg, 82%) as a colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.19 (s, 2H), 5.65 (dd, *J* = 7.6, 3.5 Hz, 1H), 4.73 (dt, *J* = 1.9, 0.9 Hz, 1H), 4.65 (t, *J* = 1.6 Hz, 1H), 3.76 (dd, *J* = 12.0, 7.6 Hz, 1H), 3.23 (td, *J* = 11.6, 6.9 Hz, 1H), 3.06 (dt, *J* = 9.4, 3.2 Hz, 1H), 2.47 − 2.37 (m, 2H), 2.34 (s, 3H), 2.12 − 2.03 (m, 2H), 2.01 (s, 3H), 1.69 (s, 3H), 1.57 − 1.50 (m, 2H), 1.35 − 1.24 (m, 4H), 0.88 (t, *J* = 6.9 Hz, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 211.4, 171.3, 155.2, 145.2, 143.4, 128.7, 111.5, 110.0, 80.9, 57.2, 47.3, 45.4, 35.6, 32.6, 31.7, 30.7, 28.9, 22.7, 21.3, 19.8, 14.2. **HRMS-ESI** *m/z* calcd for $C_{23}H_{32}NaO_5$ $[M+Na]^+$ 411.2142, found 411.2142. $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{23}}$ = −3.8º (c = 0.97, $CHCl_3$).

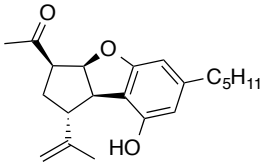
Chapter 1. Synthesis of (−)-Cannabimovone and Structural Reassignment of Anhydrocannabimovone

Oxy-Michael addition



K_2CO_3 (17 mg, 0.12 mmol, 4 equiv) was added to a solution of ketone **43** (12 mg, 0.03 mmol, 1 equiv) in MeOH (1 mL), and stirred for 15 min at 25 ºC. The crude was filtrated to remove the remaining K_2CO_3, the solvent was evaporated and the residue was purified by column chromatography (cyclohexane / EtOAc 8 : 2) to yield anhydrocannabimovone **9** (6.1 mg, 60%) and anhydrocannabimovone **9´** (1.9 mg, 19%).

Anhydrocannabimovone (9)

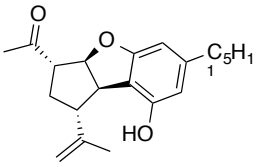


White solid.

Single crystals suitable for X-ray diffraction were grown in a saturated solution in CH_2Cl_2/cyclohexane.

M.p. 45−47 ºC. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 6.16 (s, 1H), 6.12 (s, 1H), 5.53 (dd, *J* = 7.8, 5.9 Hz, 1H), 4.87 (bs, 1H), 4.71 (bs, 1H), 3.95 (dd, *J* = 7.7, 2.2 Hz, 1H), 3.22 (dt, *J* = 12.0, 6.2 Hz, 1H), 2.83 (d, *J* = 7.5 Hz, 1H), 2.49 - 2.42 (m, 2H), 2.32 (s, 3H), 2.10 (ddd, *J* = 13.4, 11.8, 7.6 Hz, 1H), 1.88 − 1.86 (m, 1H), 1.85 (s, 3H), 1.84 − 1.78 (m, 1H), 1.55 − 1.52 (m, 2H), 1.35 − 1.26 (m, 4H), 0.88 (t, *J* = 7.0 Hz, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 206.2, 161.6, 151.9, 148.1, 145.7, 112.8, 109.6, 108.3, 102.4, 88.5, 57.5, 50.5, 49.6, 36.1, 31.6, 31.1, 30.1, 29.0, 22.7, 22.5, 14.2. **HRMS-ESI** *m/z* calcd for $C_{21}H_{28}NaO_3$ $[M+Na]^+$ 351.1931, found 351.1930. $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{22}}$ = +40.6º (c = 0.29, $CHCl_3$).

Anhydrocannabimovone (9´)

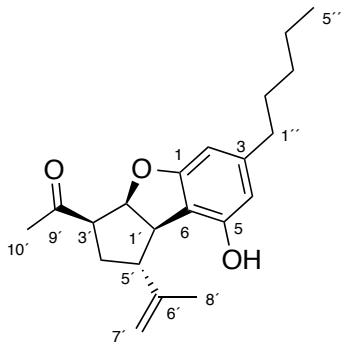


White solid.

M.p. 124−127 ºC. **^{1}H NMR (**500 MHz, $CDCl_3$) δ 6.25 (s, 1H), 6.23 (s, 1H), 5.28 (dd, *J* = 10.1, 6.8 Hz, 1H), 5.16 (bs, 1H), 5.02 (bs, 1H), 5.01 (s, 1H), 3.83 (dd, *J* = 10.1, 8.9 Hz, 1H), 3.18 (dt, *J* = 13.0, 6.5 Hz, 1H), 2.80 (ddd, *J* = 12.5, 8.8, 5.7 Hz, 1H), 2.53 − 2.46 (m, 2H), 2.33 (s, 3H), 2.06 (dt, *J* = 12.3, 6.0 Hz, 1H), 1.88 (s, 3H), 1.80 (q, *J* = 12.6 Hz, 1H), 1.62 − 1.55 (m, 2H), 1.35 − 1.27 (m, 4H), 0.88 (t, *J* = 6.9 Hz, 2H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 208.1, 160.7,

152.8, 147.9, 146.1, 112.9, 112.5, 108.9, 102.7, 89.2, 60.5, 54.9, 48.6, 36.2, 34.1, 31.6, 31.1, 30.2, 22.7, 19.8, 14.2. **HRMS-ESI** *m/z* calcd for $C_{21}H_{28}NaO_3$ $[M+Na]^+$ 351.1931, found 351.1923. $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{22}}$ = +97.0º (c = 0.38, $CHCl_3$).

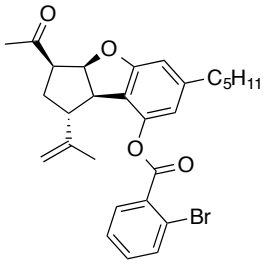
Table 12: Comparison with NMR data of isolated anhydrocannabimovone



Position	^{13}C NMR of isolated anhydrocannabimovone (d ppm)[12]	^{13}C NMR of our synthetic anhydrocannabimovone (d ppm)
5´´	14.3	14.2 (−0.1)
8´	20.7	22.5 (+1.8)
4´´	23.6	22.7 (−0.9)
4´	27.4	29.0 (+1.6)
10´	28.5	30.1 (+1.6)
2´´	31.1	31.1 (0)
3´´	32.3	31.6 (−0.7)
1´´	35.7	36.1 (+0.4)
5´	50.6	49.6 (−1.0)
1´	56.0	50.5 (−5.5)
3´	57.4	57.5 (+0.1)
2´	91.2	88.5 (−2.7)
2	102.3	102.4 (+0.1)
4	108.2	108.3 (+0.1)
7´	109.7	109.5 (−0.2)
6	115.7	112.8 (−2.9)
3	145.4	145.7 (+0.3)
6´	148.3	148.1 (−0.2)
5	157.9	151.9 (−6.0)

Chapter 1. Synthesis of (−)-Cannabimovone and Structural Reassignment of Anhydrocannabimovone

(1*R*,3*R*,3a*S*,8b*R*)-3-acetyl-6-pentyl-1-(prop-1-en-2-yl)-2,3,3a,8b-tetrahydro-1*H*-cyclopenta[*b*]benzofuran-8-yl 2-bromobenzoate (44)



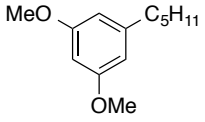
DMAP (1.2 mg, 0.01 mmol, 0.5 equiv), 2-bromobenzoic acid (4.4 mg, 0.02 mmol, 1.1 equiv) and EDC·HCl (5.7 mg, 0.03 mmol, 1.5 equiv) was added to a solution of anhydrocannabimovone **9** (6.5 mg, 0.02 mmol, 1 equiv) in CH_2Cl_2 (1.2 mL). After stirring for 24 h, CH_2Cl_2 (10 mL) was added and the organic layer was washed with HCl 10% (5 mL), $NaHCO_3$ (5 mL) and brine (5 mL). Then, the solution was dried over Na_2SO_4 and evaporated. The residue was purified by column chromatography (pentane / Et_2O 9 : 1 to 8 : 2) to afford ester **44** (7.2 mg, 71%) as a white solid.

Single crystals suitable for X-ray diffraction were grown by evaporation of a saturated solution in Et_2O/pentane.

M.p. 99 - 102 ºC. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.97 − 7.93 (m, 1H), 7.76 − 7.71 (m, 1H), 7.44 − 7.37 (m, 2H), 6.58 (s, 1H), 6.48 (s, 1H), 5.60 − 5.54 (m, 1H), 4.75 (s, 1H), 4.59 (s, 1H), 4.02 (d, *J* = 7.5 Hz, 1H), 3.17 (dt, *J* = 12.4, 6.1 Hz, 1H), 2.77 (d, *J* = 7.8 Hz, 1H), 2.57 − 2.52 (m, 2H), 2.33 (s, 3H), 2.10 (td, *J* = 13.0, 7.6 Hz, 1H), 1.81 (ddd, *J* = 13.5, 6.3, 1.3 Hz, 1H), 1.64 (s, 3H), 1.61 − 1.55 (m, 2H), 1.35 − 1.28 (m, 4H), 0.89 (t, *J* = 6.8 Hz, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 205.8, 163.8, 161.6, 147.2, 146.7, 145.7, 134.9, 133.4, 132.0, 131.2, 127.4, 122.6, 119.3, 114.2, 109.8, 107.4, 88.7, 57.5, 50.7, 50.1, 36.1, 31.6, 31.0, 29.9, 28.8, 22.7, 22.5, 14.2. **HRMS-ESI** *m/z* calcd for $C_{28}H_{31}BrNaO_4$ $[M+Na]^+$ 533.1298, found 533.1285. $[\boldsymbol{\alpha}]_{\boldsymbol{D}}^{\mathbf{23}}$ = +71.7º (c = 0.67, $CHCl_3$).

Details on unsuccessful approaches:

1,3-Dimethoxy-5-pentylbenzene (19)

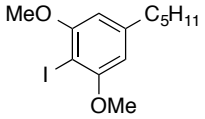


K_2CO_3 (910 g, 6.6 mmol, 2.2 equiv) and MeI (1.06 g, 7.5 mmol, 2.5 equiv) was added to a solution of olivetol (540 g, 3 mmol, 1 equiv) in DMF (10 mL) at 0 ºC. The reaction mixture was stirred for 16 h at 25 °C. After extractive work-up (H_2O / Et_2O), the residue was purified by column chromatography (cyclohexane / EtOAc, 9 : 1) to yield **19** (611mg, 98%) as a yellow oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.36 (d, *J* = 2.3 Hz, 2H), 6.31 (t, *J* = 2.3 Hz, 1H), 3.80 (s, 6H), 2.63 − 2.48 (m, 2H), 1.68 − 1.58 (m, 2H), 1.40 − 1.28 (m, 4H), 0.92 (t, *J* = 7.0 Hz, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 160.7, 145.4, 106.5, 97.5, 55.2, 36.3, 31.5, 30.9, 22.5, 14.2.

NMR data were in accordance with those previously reported.[40]

2-Iodo-1,3-dimethoxy-5-pentylbenzene (13)



n-BuLi (1.28 mL, 3.20 mmol, 2.5 M in hexanes, 1.1 equiv) was added to a solution of 1,3-dimethoxy-5-pentylbenzene (600 mg, 2.88 mmol, 1 equiv) in THF (14 mL) at 0 ºC under argon atmosphere and stirred for 15 min. Then, I_2 (878 mg, 3.46 mmol, 1.2 equiv) as a solution in THF (1.4 mL) was added and the reaction mixture was stirred for 2 h. MeOH (5 mL) was added and the crude was concentrated. After extractive work-up (H_2O / EtOAc), the organic layer was washed with saturated $Na_2S_2O_3$ (20 mL) and brine (20 mL), dried with Na_2SO_4 and evaporated. The residue was purified by column chromatography (cyclohexane / EtOAc, 9 : 1) to yield **13** (865.7 mg, 2.59 mmol, 90%) as a yellow oil.

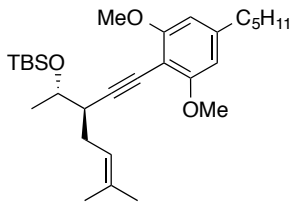
^{1}H NMR (400 MHz, $CDCl_3$) δ 6.35 (s, 2H), 3.89 (s, 6H), 2.65 – 2.56 (m, 2H), 1.70 − 1.58 (m, 2H), 1.39 − 1.31 (m, 4H), 0.90 (t, *J* = 7.0 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 159.2, 145.5, 104.5, 56.5, 36.4, 31.5, 31.1, 22.5, 14.0.

NMR data were in accordance with those previously reported.[41]

(40) Trost, B. M.; Dogra, K., *Org. Lett*. **2007**, *9*, 861–863.
(41) Klotter, F.; Studer, A. *Angew. Chem. Int. Ed.* **2015**, *54*, 8547–8550.

Chapter 1. Synthesis of (−)-Cannabimovone and Structural Reassignment of Anhydrocannabimovone

tert-butyl(((2_S_,3_R_)-3-((2,6-dimethoxy-4-pentylphenyl)ethynyl)-6-methylhept-5-en-2-yl)oxy)dimethylsilane (12)

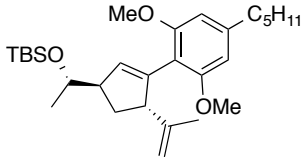


$[Pd(PPh_3)_2Cl_2]$ (21 mg, 0.03 mmol, 0.05 equiv) was added to a solution of 2-iodo-1,3-dimethoxy-5-pentylbenzene (200mg, 0.60 mmol, 1 equiv) in a mixture of degassed (freeze-pump 3 cycles) Et_3N and $^iPr_2NH$ (1 : 1, 2 mL) 25 ºC under argon atmosphere and stirred for 15 min, CuI (11.5 mg, 0.06 mmol, 0.1 equiv) and stirred for 15 min and finally enyne **14** (176 mg, 0.66 mmol, 1.1 equiv) in solution (2 mL) dropwise. The mixture was stirred at room temperature for 16 h. The reaction was treated with saturated solution of NH_4Cl (10 mL) and extracted with CH_2Cl_2 (3 × 30 mL). The combined organic phases were washed with brine (20 mL), dried over Na_2SO_4 and purified by column chromatography (pentane to pentane / ether, 95 : 5) to give enyne **12** (231mg, 0.49 mmol, 81%) as a pale yellow oil.

Note: the reaction preferentially should be set up in glovebox.

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.34 (s, 2H), 5.45 (ddt, *J* = 8.0, 6.7, 1.4 Hz, 1H), 4.11 (qd, *J* = 6.2, 4.1 Hz, 1H), 3.85 (s, 6H), 2.72 (dt, *J* = 10.1, 4.3 Hz, 1H), 2.61 − 2.52 (m, 2H), 2.48 (ddd, *J* = 13.0, 7.7, 4.5 Hz, 1H), 2.26 − 2.18 (m, 1H), 1.74 (d, *J* = 1.4 Hz, 3H), 1.69 − 1.55 (m, 5H), 1.25 (m, 7H), 0.95 − 0.88 (m, 9H + 3H), 0.09 (s, 3H), 0.07 (s, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 161.2, 144.3, 132.1, 123.1, 104.0, 99.9, 99.2, 74.9, 70.0, 56.0, 41.4, 36.8, 31.5, 31.0, 27.4, 25.9, 25.8, 22.5, 19.5, 18.1, 17.9, 14.0, −4.5, −4.8. **HRMS-ESI** *m/z* calcd for $C_{29}H_{48}O_3NaSi$ $[M+Na]^+$ 495.3265, found 495.3266.

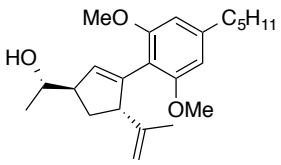
tert-butyl((_S_)-1-((1_R_,4_S_)-3-(2,6-dimethoxy-4-pentylphenyl)-4-(prop-1-en-2-yl)cyclopent-2-en-1-yl)ethoxy)dimethylsilane (11)



$[JohnPhosAu(NCMe)]SbF_6$ (11.6 mg, 0.015 mmol, 0.05 equiv) was added to a solution of enyne **12** (142 mg, 0.3 mmol, 1 equiv) in DMSO (5 mL, 0.5 M) and stirred at 25 ºC for 5 h under inert atmosphere. The reaction mixture was treated with brine and extracted with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography (cyclohexane / EtOAc, 50 : 1) to give cyclopentene **11** (121.8 mg, 0.258 mmol, 86%) as pale yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.36 (s, 2H), 5.85 (t, *J* = 2.1 Hz, 1H), 4.59 (dt, *J* = 2.8, 0.8 Hz, 1H), 4.48 (dt, *J* = 2.8, 1.4 Hz, 1H), 4.00 (ddt, *J* = 8.9, 4.6, 2.2 Hz, 1H), 3.75 − 3.66 (m, 7H), 2.96 (dddd, *J* = 8.4, 6.7, 5.4, 2.4 Hz, 1H), 2.60 - 2.52 (m, 2H), 1.95 (ddd, *J* = 13.1, 9.1, 5.9 Hz, 1H), 1.84 (ddd, *J* = 13.2, 8.5, 4.8 Hz, 1H), 1.70 – 1.54 (m, 5H), 1.39 − 1.33 (m, 4H), 1.16 (d, *J* = 6.1 Hz, 3H), 0.96 – 0.88 (m, 12H), 0.06 (s, 3H), 0.05 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 158.0, 148.7, 142.8, 138.6, 134.0, 113.4, 109.6, 104.3, 72.2, 56.7, 55.2, 53.6, 36.6, 32.2, 31.8, 31.0, 25.9, 22.6, 21.3, 19.0, 18.1, 14.1, −4.3, −4.7. **HRMS-ESI** *m/z* calcd for $C_{29}H_{48}O_3NaSi$ $[M+Na]^+$ 495.3324, found 495.3324.

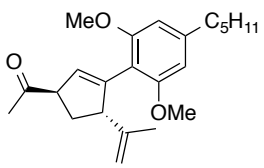
(*S*)-1-((1*R*,4*S*)-3-(2,6-dimethoxy-4-pentylphenyl)-4-(prop-1-en-2-yl)cyclopent-2-en-1-yl)ethan-1-ol (S9)



1M TBAF solution in THF (0.5 mL, 0.5 mmol, 2 equiv) was added to a solution of the protected alcohol **11** (118 mg, 0.25 mmol, 1 equiv) in dry THF (2 mL) at 25 °C. The reaction was stirred for 18 h at 25 °C then mixture quenched with brine (5 mL) and aqueous phase was extracted with CH_2Cl_2 (3 × 15 mL). The combined organic layers were washed with brine, dried over Na_2SO_4 and purified by column chromatography (cyclohexane / EtOAc, 1 : 15 to 1 : 10) to give the free alcohol (85 mg, 0.238 mmol, 95%) as a white solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.37 (s, 2H), 5.85 (t, *J* = 2.1 Hz, 1H), 4.61 (dt, *J* = 2.7, 0.8 Hz, 1H), 4.51 (dq, *J* = 2.8, 1.4 Hz, 1H), 4.03 (ddt, *J* = 8.6, 6.4, 2.2 Hz, 1H), 3.75 − 3.66 (m, 7H), 2.99 (dddq, *J* = 8.1, 4.9, 2.4 Hz, 1H), 2.62 - 2.53 (m, 2H), 2.09 – 1.97 (m, 2H), 1.87 (br s, 1H), 1.74 – 1.56 (m, 5H), 1.41 − 1.29 (m, 4H), 1.20 (d, *J* = 6.4 Hz, 3H), 0.98 – 0.88 (m, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 157.6, 147.9, 143.3, 142.5, 130.5, 112.8, 110.3, 104.1, 71.8, 55.6, 55.5, 52.5, 36.6, 33.4, 31.7, 31.0, 22.5, 21.9, 18.8, 14.0. **HRMS-ESI** *m/z* calcd for $C_{23}H_{34}O_3Na$ $[M+Na]^+$ 381.2400, found 381.2406.

(*S*)-1-((1*R*,4*S*)-3-(2,6-dimethoxy-4-pentylphenyl)-4-(prop-1-en-2-yl)cyclopent-2-en-1-yl)ethan-1-one (20)

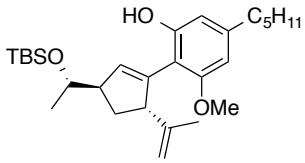


$NaHCO_3$ (48.3 mg, 0.575 mmol, 2.5 equiv) was added to a solution of alcohol **S9** (82 mg, 0.23 mmol, 1 equiv) in 2.5 mL of HPLC grade CH_2Cl_2 under argon atmosphere. The suspension was cooled down to 0°C. DMP (107.3 mg, 0.253 mmol, 1.1 equiv) was added to the

reaction mixture in 1 portion. The mixture was stirred for 5 h at 25 ºC. The reaction mixture was diluted with CH_2Cl_2 (10 mL), and then washed with aqueous saturated $NaHCO_3$ (2 × 20 mL), followed by brine (10 mL). The organic phase was dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography (cyclohexane / EtOAc, 20 : 1) to give **20** (70.4 mg, 0.198 mmol, 86%) as a pale yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.36 (s, 2H), 5.85 (dd, *J* = 2.5, 2.1 Hz, 1H), 4.64 (dt, *J* = 2.6, 0.8 Hz, 1H), 4.54 (dq, *J* = 2.8, 1.4 Hz, 1H), 4.22 – 4.11 (m, 1H), 3.75 − 3.66 (m, 7H), 2.60 − 2.53 (m, 2H), 2.47 (ddd, *J* = 13.4, 9.0, 5.0 Hz, 1H), 2.20 (s, 3H), 2.01 (ddd, *J* = 13.3, 9.0, 5.7 Hz, 1H), 1.68 – 1.54 (m, 5H), 1.41 − 1.29 (m, 4H), 0.95 – 0.85 (m, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 209.9, 157.8, 147.3, 143.6, 142.0, 129.4, 112.0, 110.7, 104.2, 59.3, 55.6, 54.7, 36.6, 31.8, 31.7, 31.0, 27.6, 22.5, 18.9, 14.0. **HRMS-ESI** *m/z* calcd for $C_{23}H_{32}O_3Na$ $[M+Na]^+$ 379.2244, found 379.379.2258.

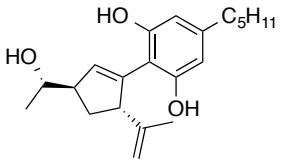
2-((3*R*,5*S*)-3-((*S*)-1-((*tert*-butyldimethylsilyl)oxy)ethyl)-5-(prop-1-en-2-yl)cyclopent-1-en-1-yl)-3-methoxy-5-pentylphenol (22)



The ketone **20** (10 mg, 0.028 mmol, 1 equiv) as a solution in dry diethyl ether was added to solution of MeMgI (prepeared in situ from magnesium (13 mg, 0.56 mmol, 20 equiv) and MeI (35 μL, 0.56 mmol, 20 equiv) in 1 mL of dry diethyl ether) at 25 ºC under argon atmosphere. All volatiles were removed under reduced pressure and reaction mixture was solely warmed to 160 ºC. The mixture was stirred for 30 min and cooled down to 25 ºC. Then quenched by slow addition of aqueous saturated NH_4Cl (2 mL), followed by brine (2 mL), product was extracted with CH_2Cl_2 (2 × 5 mL). The organic phase was dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by preparative TLC (cyclohexane / EtOAc, 7 : 1) to give **22** (4.9 mg, 0.014 mmol, 51%) as a pale yellow oil.**^{1}H NMR** (400 MHz, $CDCl_3$) δ 6.42 (d, *J* = 1.4 Hz, 1H), 6.23 (d, *J* = 1.4 Hz, 1H), 5.93 (t, *J* = 2.0 Hz, 1H), 5.80 (s, 1H), 4.61 (dt, *J* = 2.4, 0.8 Hz, 1H), 4.58 (dq, *J* = 2.8, 1.5 Hz, 1H), 4.04 − 3.97 (m, 1H), 3.83 − 3.70 (m, 4H), 2.96 (dtt, *J* = 8.2, 5.4, 2.4 Hz, 1H), 2.56 − 2.49 (m, 2H), 2.05 – 1.90 (m, 2H), 1.66 − 1.54 (m, 5H), 1.37 − 1.20 (m, 4H), 1.18 (d, *J* = 6.1 Hz, 3H), 0.90 (s, 12H), 0.07 (s, 3H), 0.05 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 157.6, 153.4, 147.4, 144.0, 141.2, 133.6, 110.7, 110.1, 107.6, 103.0, 71.9, 55.3, 55.2, 53.3, 36.3, 32.6, 31.7, 30.8, 25.9, 22.6, 21.8, 19.1, 18.1, 14.0, −4.3, −4.7.

Chapter 1. Synthesis of (−)-Cannabimovone and Structural Reassignment of Anhydrocannabimovone

2-((3*R*,5*S*)-3-((*S*)-1-hydroxyethyl)-5-(prop-1-en-2-yl)cyclopent-1-en-1-yl)-5-pentylbenzene-1,3-diol (31)

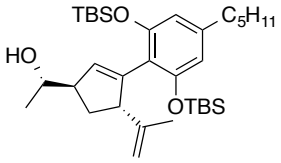


0.5 M aqueous solution of HCl (400 µL) was added to a solution of protected alcohol **27** (47.2 mg, 0.1 mmol, 1 equiv) in MeOH (4.5 mL) at 25 ºC. The reaction mixture was stirred at 40 ºC for 16 h. The reaction mixture was diluted with CH_2Cl_2 (20 mL), and then washed with aqueous saturated $NaHCO_3$ (2 × 20 mL), followed by brine (10 mL). The organic phase was dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by preparative TLC (cyclohexane / EtOAc, 1 : 1) to give titled compound **31** (16.8 mg, 0.05 mmol, 51%) as a pale yellow oil.

Note: Free diphenol can be isolated as individual compound but for convenience the crude product was directly used the following step.

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.30 (s, 2H), 6.04 (t, *J* = 1.9 Hz, 1H), 5.64 (br s, 2H), 4.84 (dt, *J* = 1.8, 0.9 Hz, 1H), 4.78 (t, *J* = 1.6 Hz, 1H), 3.89 (qd, *J* = 6.4, 4.2 Hz, 1H), 3.83 (ddt, *J* = 8.2, 6.6, 2.2 Hz, 1H), 3.02 (ddq, *J* = 10.4, 6.4, 2.3 Hz, 1H), 2.53 − 2.41 (m, 2H), 2.15 – 2.08 (m, 2H), 1.67 (t, *J* = 1.1 Hz, 3H), 1.63 – 1.52 (m, 2H), 1.37 – 1.29 (m, 4H), 1.27 (t, *J* = 6.3 Hz, 3H), 0.90 (t, *J* = 7.1 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ153.6, 148.5, 144.6, 142.4, 134.1, 111.4, 109.0, 107.5, 71.4, 55.0, 51.9, 35.7, 34.3, 31.5, 30.6, 22.5, 22.3, 20.9, 14.0.

(*S*)-1-((1*R*,4*S*)-3-(2,6-bis((*tert*-butyldimethylsilyl)oxy)-4-pentylphenyl)-4-(prop-1-en-2-yl)cyclopent-2-en-1-yl)ethan-1-ol (32)

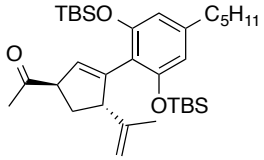


DBU (16 µL, 0.105 mmol, 2.1 equiv) and TBSCl (16.6 mg, 0.11 mmol, 2.2 equiv) were added to a solution of **31** (16.8 mg, 0.5 mmol, 1 equiv) in CH_2Cl_2 (2.5 mL) at 0 ºC under argon atmosphere. The reaction was stirred 16 h at 25 ºC. The mixture was quenched with 0.5M HCl solution (3 mL) and the aqueous phase was extracted with CH_2Cl_2 (2 × 5 mL). The combined organic phases were washed with brine, dried over Na_2SO_4 and purified by preparative TLC (cyclohexane / EtOAc, 7 : 1) to give **32** (23.1 mg, 0.043 mmol, 86%) as a colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.25 (s, 2H), 5.88 (t, *J* = 2.0 Hz, 1H), 4.88 (d, *J* = 2.5 Hz, 1H) 4.52 (dt, *J* = 2.7, 1.4 Hz, 1H), 4.12 (m, 1H), 3.72 – 3.64 (m, 1H), 2.91 (dqt, *J* = 7.8, 5.0, 2.2 Hz, 1H), 2.45 (t, *J* = 7.6 Hz, 2H), 1.93 (dd, *J* = 7.8, 6.5 Hz, 2H), 1.62 – 1.56

(m, 5H), 1.40 − 1.26 (m, 4H), 1.23 (d, *J* = 6.2 Hz, 3H), 0.92 (s, 18H), 0.90 (t, *J* = 7.0 Hz, 3H), 0.25 (s, 6H), 0.21 (s, 6H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ154.1, 148.0, 142.1, 141.7, 131.6, 117.5, 111.8, 110.1, 71.5, 54.2, 53.1, 35.7, 32.9, 31.3, 30.6, 25.9, 22.5, 22.0, 20.0, 18.4, 14.0, −3.9, −3.9.

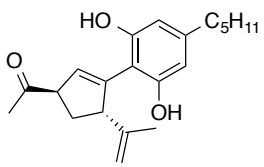
1-((1*R*,4*S*)-3-(2,6-bis((*tert*-butyldimethylsilyl)oxy)-4-pentylphenyl)-4-(prop-1-en-2-yl)cyclopent-2-en-1-yl)ethan-1-one (33)



$NaHCO_3$ (8.8 mg, 0.105 mmol, 2.5 equiv) was added to a solution of alcohol **32** (22.5 mg, 0.042 mmol, 1 equiv) in 1 mL of HPLC grade CH_2Cl_2 under argon atmosphere. The suspension was cooled down to 0 °C. DMP (19.6 mg, 0.046 mmol, 1.1 equiv) was added to the reaction mixture in 1 portion. The mixture was stirred for 5 h at 25 ºC. The reaction mixture was diluted with CH_2Cl_2 (10 mL), and then washed with aqueous saturated $NaHCO_3$ (2 × 5 mL), followed by brine (5 mL). The organic phase was dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by preparative TLC (cyclohexane / EtOAc, 7 : 1) to give **33** (18.2 mg, 0.034 mmol, 80%) as a pale yellow oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.25 (s, 2H), 5.85 (t, *J* = 2.2 Hz, 1H), 4.70 (dt, *J* = 2.5, 08 Hz, 1H) 4.55 (dt, *J* = 2.7, 1.4 Hz, 1H), 4.18 (ddt, *J* = 9.1, 4.6, 2.3 Hz, 1H), 3.75 (ddt, *J* = 8.6, 5.6, 2.6 Hz, 1H), 2.50 (ddd, *J* = 13.3, 9.3, 5.9 Hz, 1H), 2.45 (dd, *J* = 8.2, 6.9 Hz, 2H), 1.98 (ddd, *J* = 13.6, 8.9, 4.9 Hz, 1H), 1.60 – 1.52 (m, 5H), 1.38 − 1.26 (m, 4H), 1.23 (d, *J* = 6.2 Hz, 3H), 0.98 (s, 18H), 0.90 (t, *J* = 7.1 Hz, 3H), 0.24 (s, 6H), 0.19 (s, 6H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 208.9, 154.0, 147.2, 142.4, 142.4, 129.2, 117.0, 111.9, 110.7, 59.0, 53.9, 35.7, 31.4, 31.3, 30.6, 28.0, 25.9, 22.5, 20.0, 18.3, 14.0, −3.9, −4.1. **HRMS-ESI** *m/z* calcd for $C_{33}H_{56}O_3Si_2Na$ $[M+Na]^+$ 579.3660, found 579.3656.

1-((1*R*,4*S*)-3-(2,6-dihydroxy-4-pentylphenyl)-4-(prop-1-en-2-yl)cyclopent-2-en-1-yl)ethan-1-one (34)



HF•Py (7 µL, 0.28 mmol, 10 equiv) was added to a solution of protected phenol **33** (15.1 mg, 0.028 mmol, 1 equiv) in HPLC grade THF (2 mL) at 0 ºC. The reaction mixture was for 15 h at 25 ºC Then quenched by slow addition of aqueous saturated $NaHCO_3$ (5 mL), followed by brine (2 mL), product was extracted with CH_2Cl_2 (2 × 5 mL). The organic phase was dried over Na_2SO_4 and concentrated under reduced

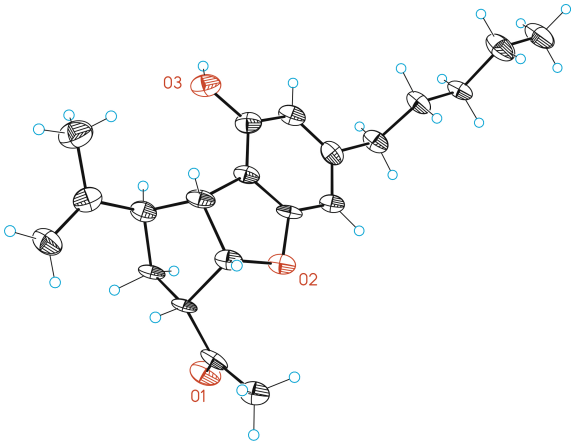
pressure. The residue was purified by preparative TLC (cyclohexane / EtOAc, 7 : 1) to give **34** (5.3 mg, 0.016 mmol, 58%) as a pale yellow oil.

Note: reaction performed in plastic vial.

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.30 (s, 2H), 5.96 (t, *J* = 2.0 Hz, 1H), 5.45 (br s, 2H), 4.83 (dt, *J* = 1.8, 0.9 Hz, 1H) 4.80 (dt, *J* = 1.6, 0.8 Hz, 1H), 3.97 – 3.87 (m, 2H), 2.50 − 2.45 (m, 2H), 2.43 (td, *J* = 8.6, 4.2 Hz, 1H), 2.27 (s, 3H), 2.21 (ddd, *J* = 13.5, 9.0, 6.7 Hz, 1H), 1.65 (dd, *J* = 1.5, 0.8, Hz, 3H), 1.63 – 1.53 (m, 2H), 1.37 − 1.26 (m, 4H), 0.90 (t, *J* = 6.9 Hz, 3H).

Crystallographic data:

Crystallographic data for compound 9



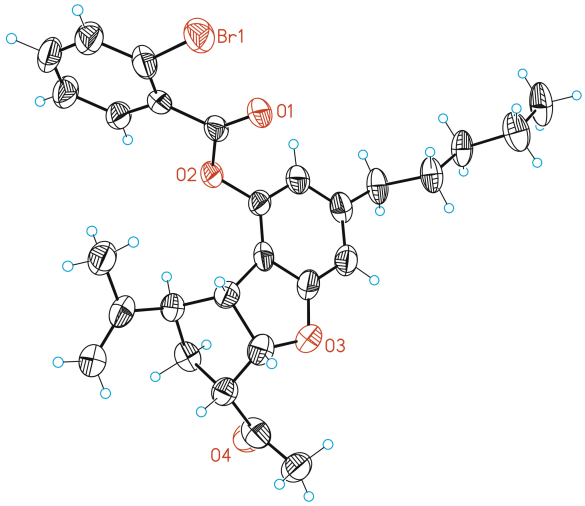
This CIF file was deposited with Cambridge Crystallographic Data Center: CCDC1454956

Table S4. Crystal data and structure refinement for **9**.

Empirical formula	C24 H34 O3	
Formula weight	370.51	
Temperature	100(2) K	
Wavelength	0.71073 Å	
Crystal system	Orthorhombic	
Space group	P2(1)2(1)2	
Unit cell dimensions	a = 16.937(3)Å	α= 90°.
	b = 25.771(5)Å	β = 90°.
	c = 4.9287(10)Å	γ = 90°.
Volume	2151.3(7) Å3	
Z	4	
Density (calculated)	1.144 Mg/m3	
Absorption coefficient	0.073 mm-1	
F(000)	808	
Crystal size	0.25 x 0.10 x 0.02 mm^3	
Theta range for data collection	1.580 to 23.294°.	
Index ranges	-18<=h<=15,-28<=k<=19,-4<=l<=5	
Reflections collected	6653	
Independent reflections	3067[R(int) = 0.0684]	
Completeness to theta =23.294°	97.6%	
Absorption correction	Empirical	
Max. and min. transmission	0.999 and 0.768	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	3067/ 60/ 275	
Goodness-of-fit on F^2	1.051	

Final R indices [I>2sigma(I)]	R1 = 0.0648, wR2 = 0.1473
R indices (all data)	R1 = 0.1104, wR2 = 0.1782
Flack parameter	x =-0.8(10)
Largest diff. peak and hole	0.290 and -0.348 e.Å^{-3}

Crystallographic data for compound 44



This CIF file was deposited with Cambridge Crystallographic Data Center: CCDC1454958

Table S5. Crystal data and structure refinement for **44**.

Empirical formula	C29.25 H34 Br O4	
Formula weight	529.47	
Temperature	100(2) K	
Wavelength	0.71073 Å	
Crystal system	Orthorhombic	
Space group	P2(1)2(1)2	
Unit cell dimensions	a = 5.0032(4)Å	α= 90°.
	b = 14.3132(9)Å	β = 90°.
	c = 38.066(3)Å	γ = 90°.
Volume	2725.9(3) Å3	
Z	4	
Density (calculated)	1.290 Mg/m3	
Absorption coefficient	1.539 mm-1	
F(000)	1106	
Crystal size	0.10 x 0.05 x 0.05 mm^3	
Theta range for data collection	2.570 to 25.386°.	
Index ranges	-6<=h<=4,-17<=k<=17,-45<=l<=45	
Reflections collected	23921	
Independent reflections	4955[R(int) = 0.0940]	
Completeness to theta =25.386°	99.5%	

Chapter 1. Synthesis of (−)-Cannabimovone and Structural Reassignment of Anhydrocannabimovone

Absorption correction	Multi-scan
Max. and min. transmission	0.927 and 0.507
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	4955/ 209/ 437
Goodness-of-fit on F^2	1.080
Final R indices [I>2sigma(I)]	R1 = 0.0735, wR2 = 0.1520
R indices (all data)	R1 = 0.1183, wR2 = 0.1686
Flack parameter	x =0.014(10)
Largest diff. peak and hole	0.848 and -0.511 e.Å^{-3}

UNIVERSITAT ROVIRA I VIRGILI
TOTAL SYNTHESES OF NOVEL CANNABINOIDS AND LUNDURINES A¿C WITH A GOLDEN TOUCH
Mariia Kirillova

Chapter 2. Total Synthesis of Lundurines A−C

UNIVERSITAT ROVIRA I VIRGILI
TOTAL SYNTHESES OF NOVEL CANNABINOIDS AND LUNDURINES A¿C WITH A GOLDEN TOUCH
Mariia Kirillova

Introduction

It has been more than a century since Adolf von Baeyer accomplished the first synthesis of indole in 1866 by the reduction of oxindole, obtained during the decomposition of the indigo dye.[1] Three years later he proposed its structure,[2] depicted in Figure 1.

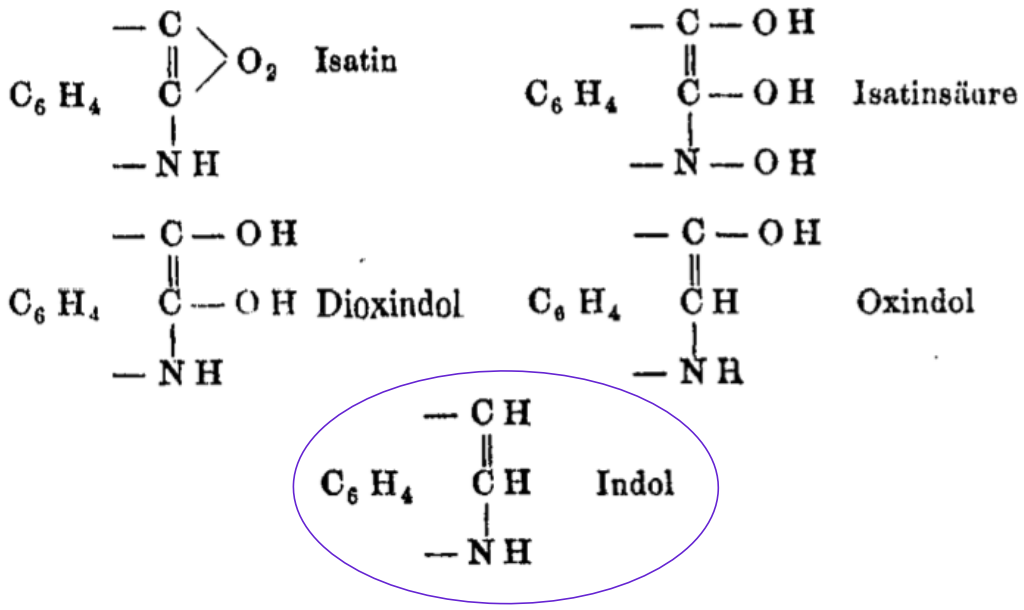


Figure 1. Baeyer's original structures, 1869.

Interestingly, the first indole alkaloid – strychnine − was isolated by Pierre Joseph Pelletier and Joseph Bienaimé Cavenou in 1818, prior to the discovery of indole itself (Figure 2).[3] The structure of strychnine was subsequently determined in 1946 by Sir Robert Robinson, who was awarded the Nobel Prize for this discovery. Later, in 1965, Robert B. Woodward was also awarded the Nobel Prize[4] for his outstanding work on total synthesis, which included the first total synthesis of strychnine,[5] one of the most renowned syntheses in the history of organic chemistry.

(1) Baeyer, A. *Justus Liebigs Ann. Der Chem*. **1866**, *140*, 295–313.
(2) Baeyer, A.; Emmerling, A. *Chem. Ber.* **1869**, *2*, 679–682.
(3) (a) Pelletier, P. J.; Caventou, J. B. *Annales de Chimie et de Physique* **1818**, *8*, 323−324. (b) Pelletier, P. J.; Caventou, J. B. *Annales de Chimie et de Physique* **1819**, *10*, 142−176.
(4) http://www.nobelprize.org/nobel_prizes/chemistry/laureates/.
(5) (a) Woodward, R. B.; Cava, M. P.; Ollis, W. D.; Hunger, A.; Daeniker, H. U.; Schenker, K. *J. Am. Chem. Soc*. **1954**, *76*, 4749–4751.

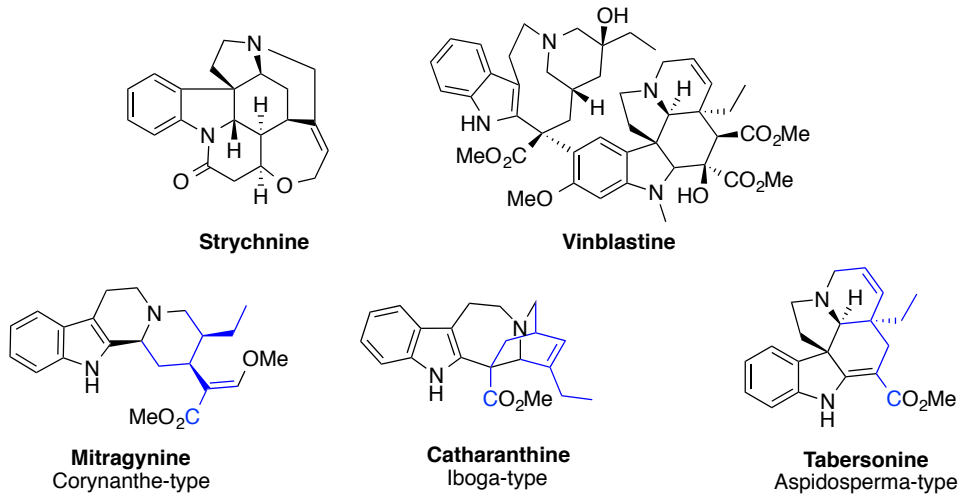


Figure 2. Indole derived alkaloids.

The indole scaffold is among the most commonly occurring structural motifs in natural products and pharmaceuticals. Most monoterpenoid indole alkaloids contain a C_9 or C_{10} fragment originating from secologanin.[6] Depending on the structure of this fragment (highlighted in blue), these alkaloids belong to the *Corynanthe*, *Iboga* and *Aspidosperma* classes, named after typical genuses or species of the plant, which contain such alkaloids (Figure 2).[7] Currently there are more than 200 known bisindole alkaloids. One of the most well-known is vinblastine, a medication used in the treatment of a number of types of cancer.[8]

Lundurines A (**1**), B (**2**), and C (**3**) belong to a relatively new class of indole alkaloids that were isolated in 1995 from *Kopsia tenuis*,[9] a plant endemic to the north of the Borneo island, which and they posses interesting cytotoxic properties.[10] These alkaloids feature a unique indoline-fused polyhydropyrroloazocine core as well as an indolylcyclopropane system (Figure 2). Related alkaloids lacking the cyclopropane ring include lapidilectam, lapidilectines, grandilodines, and tenuisines, have also been isolated from plants of the *Kopsia* genus.[11]

(6) Tietza, L.-F. *Angew. Chem. Int. Ed.* **1983**, *22*, 828–841.
(7) Mizoguchi, H.; Oikawa, H.; Oguri, H. *Nature Chem.* **2014**, *6*, 57–64.
(8) (a) "Vinblastine Sulfate". *The American Society of Health-System Pharmacists*. Retrieved Jan 2, 2015. (b) Ravina, E. "The evolution of drug discovery: from traditional medicines to modern drugs" *(1. Aufl. ed.) Weinheim: Wiley-VCH.* **2011**, 157.
(9) Kam, T.-S.; Yoganathan, K.; Chuah, C. H. *Tetrahedron Lett.* **1995**, *36*, 759–762.
(10) Kam, T.-S.; Lim, K.-H.; Yoganathan, K.; Hayashi, M.; Komiyama, K. *Tetrahedron* **2004**, *60*, 10739–10745.
(11) (a) Awang, K.; Sévenet, T.; Païs, M.; Hadim, A. H. A. *J. Nat. Prod.* **1993**, *56*, 1134–1139. (b) Yap, W.-S.; Gan, C.-Y.; Low, Y.-Y.; Choo, Y.-M.; Etoh, T.; Hayahi, M.; Komiyama, K.; Kam, T.-S. *J. Nat. Prod.* **2011**, *74*, 1309–1312.

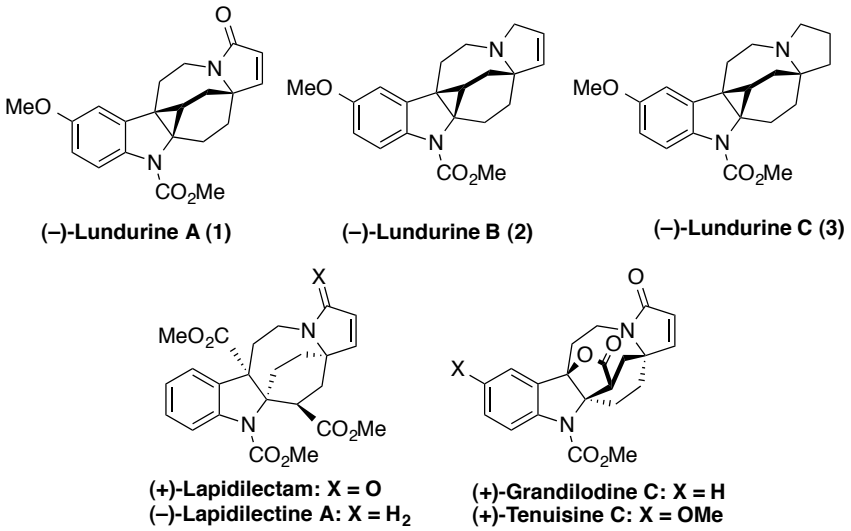
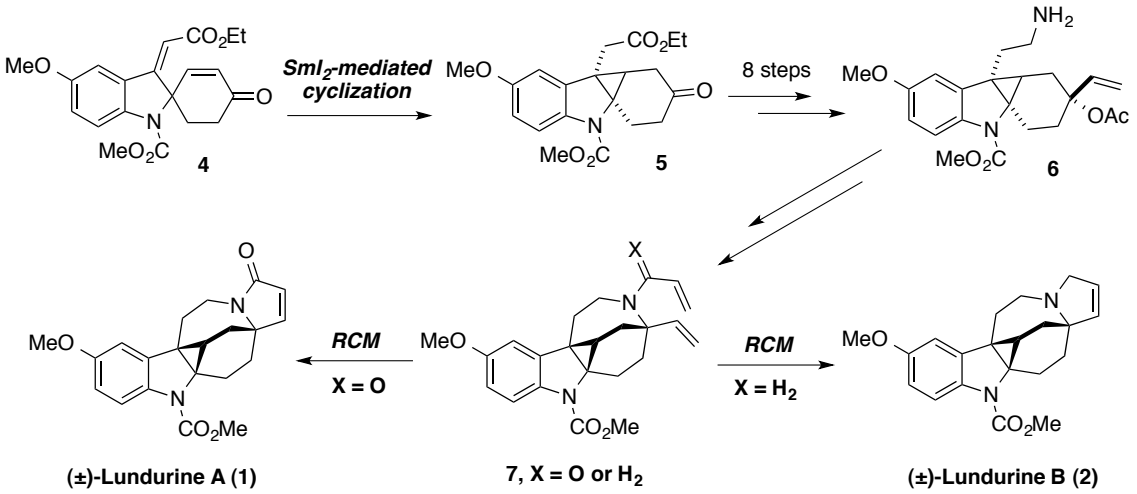


Figure 2. Selected members of the *Kopsia* alkaloid family.

The lundurines have recently attracted considerable attention from the synthetic community,[12,13,14,15,16,17] and the total syntheses of lundurine A and lundurine B have been reported.[13-17]

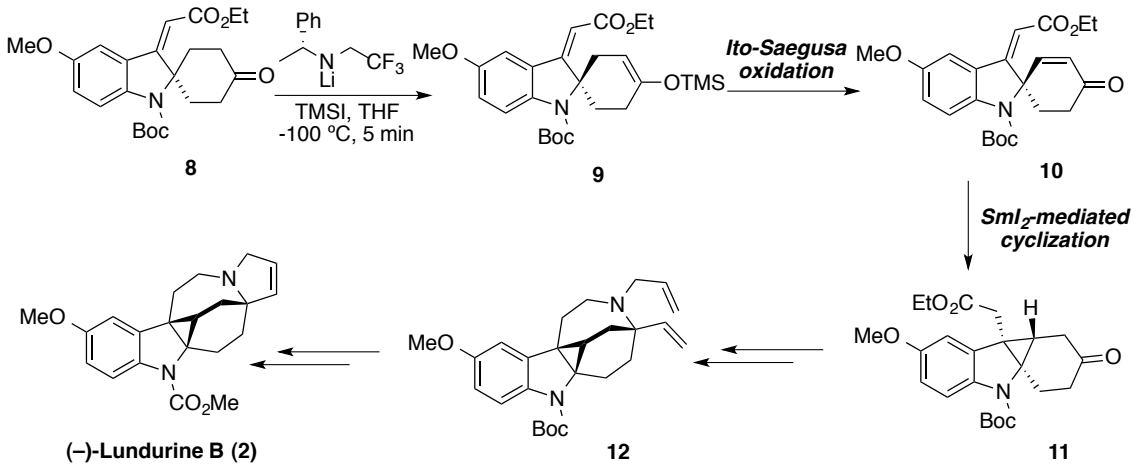
The group of Prof. Nishida accomplished the first synthesis of (±)-lundurine B in 2014.[13] Shortly after, the same strategy was applied for (±)-lundurine A as well as an improved synthesis of (±)-lundurine B (Scheme 1).[14] Their approach relied on samarium(II) iodide mediated radical cyclization of spiro-enone **4** to form cyclopropane-containing tetracycle **5**. The ester group of **5** was converted into a primary amine and the ketone moiety into the corresponding tertiary acetate in 8 linear steps. A palladium-catalyzed amination resulted in the formation of the polyhydropyrroloazocine ring system of **7**. Finally, they used a ring-closing metathesis to complete the 29-step sequence and obtained the first synthetic samples of (±)-lundurine A and (±)-lundurine B.

(12) Schultz, E. E.; Pujanauski, B. G.; Sarpong, R. *Org. Lett* **2012**, *14*, 648–651.
(13) Hoshi, M.; Kaneko, O.; Nakajima, M.; Arai, S.; Nishida, A. *Org. Lett*. **2014**, *16*, 768–771.
(14) Arai, S.; Nakajima, M.; Nishida A. *Angew. Chem. Int. Ed.* **2014**, *53*, 5569–5572.
(15) Jin, S.; Gong, J.; Qin, Y. *Angew. Chem. Int. Ed.* **2015**, *54*, 2228–2231.
(16) Nakajima, M.; Arai, S.; Nishida, A. *Chem. Asian. J.* **2015***, 10*, 1065–1070.
(17) Huang, H.-X.; Jin, S.-J.; Gong, J.; Zhang, D.; Song, H.; Qin, Y. *Chem. Eur. J.* **2015**, *21*, 13284–13290.



Scheme 1. Nishida's synthesis of (±)-lundurines A and B.

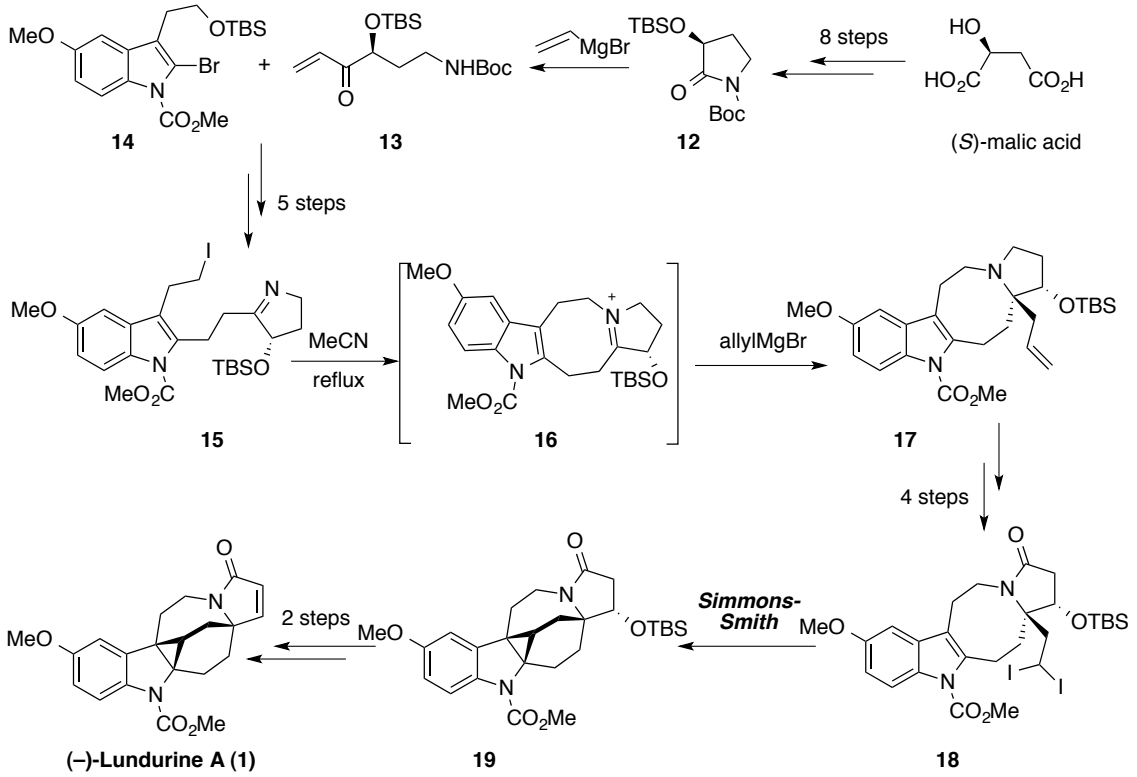
The same group accomplished the asymmetric synthesis of (−)-lundurine B one year later (Scheme 2).[16] The desymmetrization of spiro cyclohexanone **8** employing a chiral lithium amide followed by Ito-Saegusa oxidation provided the key chiral spiro-cyclohexanone **10** with 87% *ee*. The previously developed samarium(II) iodide mediated radical cyclization of enone **10** delivered Boc-protected indoline **11**. Functional group manipulations similar to those applied in their first approach, followed by a late stage ring-closing metathesis completed the 30 step synthesis of (−)-lundurine B with 1.2% overall yield.



Scheme 2. Nishida's asymmetric synthesis of (−)-lundurine B.

Shortly after the synthesis of (±)-lundurine A was disclosed, Qin's group published the first asymmetric synthesis of (−)-lundurine A and the determined its absolute configuration (Scheme 3).[15] A palladium-catalyzed Heck coupling between enone **13**

and bromoindole **14** followed by a functional group modification delivered iodide **15**. An intramolecular alkylation led to the formation of the polyhydropyrroloazocine ring and the resulting iminium ion reacted with allylmagnesium bromide to generate tetrasubstituted carbon C20. A late stage Simmons-Smith cyclopropanation efficiently constructed the hexacyclic core of **1**. This concise asymmetric synthesis of (−)-lundurine A consists of 15 linear steps, starting from pyrrolidinone **12**, and provides the natural product in approximately 2% overall yield. However, the lengthy preparation of pyrrolidinone **12**, which requires 8 additional steps,[18] makes the synthesis of large quantities of the natural products and / or analogues, for broad biological assays, impractical.

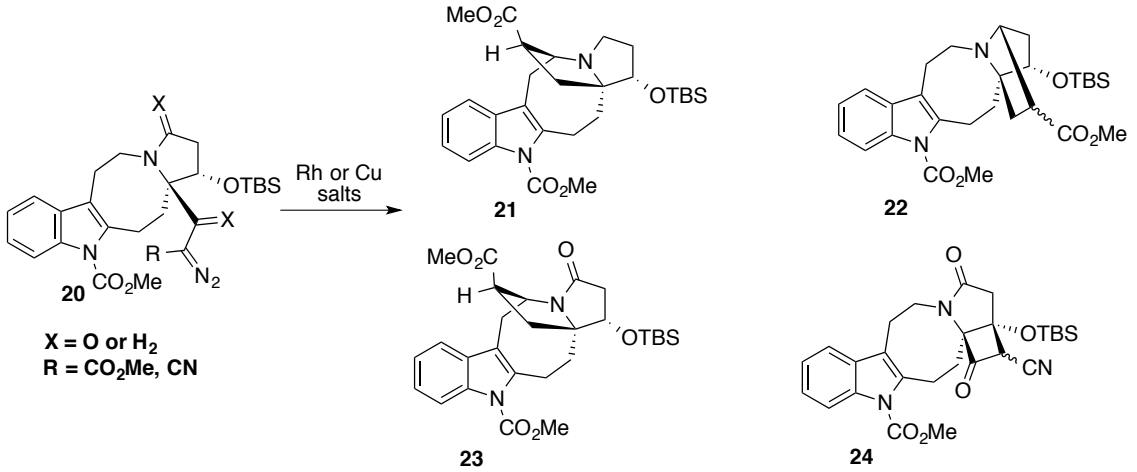


Scheme 3. Qin's asymmetric synthesis of (−)-lundurine A.

Qin's group performed an extensive investigation of the transition metal-catalyzed cyclopropanation on ring systems closely related to the lundurines.[19] A brief summary of these results will be presented in Scheme 4. This study concluded that the metalo-carbene species generated from an α-diazocyanide or α-diazocarboxylate undergoes

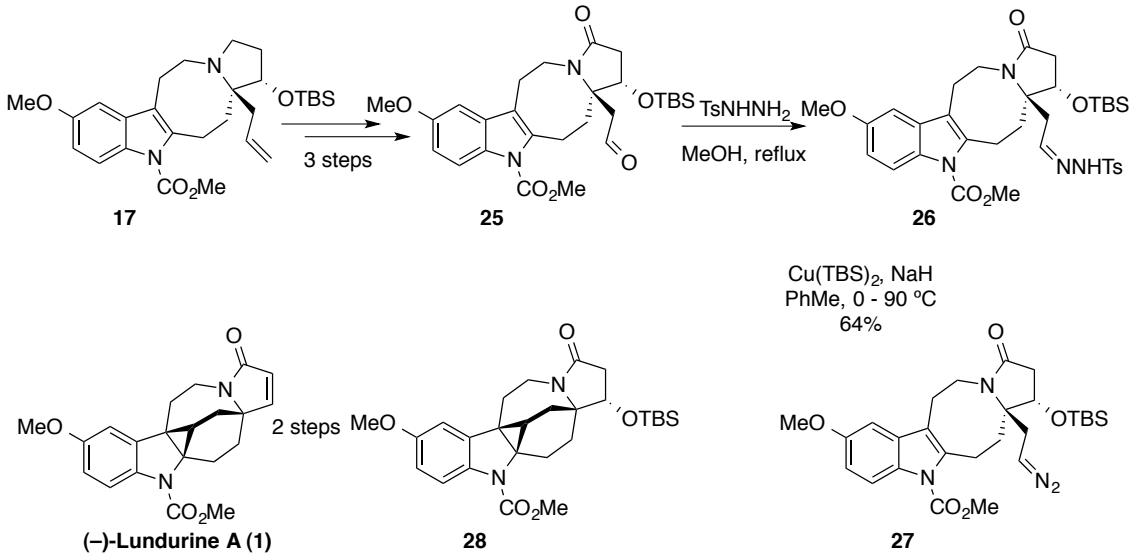
(18) Zheng, X.; Feng, C.-G.; Ye, J.-L.; Huang, P.-Q. *Org. Lett.* **2005**, *7*, 553−556.
(19) (a) Zhang D.; Song, H.; Qin Y. *Acc. Chem. Res.* **2001**, *44*, 447–457. (b) Yang, J.; Song, H.; Xiao, X.; Wang, J.; Qin Y. *Org. Lett.* **2006**, *8*, 2187–2190. (c) Song, H.; Wang, J.; Chen, W.; Qin Y. *Org. Lett.* **2006**, *8*, 6011–6014.

unexpected carbene C−H insertions. The steric hindrance, presence of electron-withdrawing groups and the conformational features of the 8-membered ring were proposed as possible explanations for the preferential formation of each of the C-H insertion products.



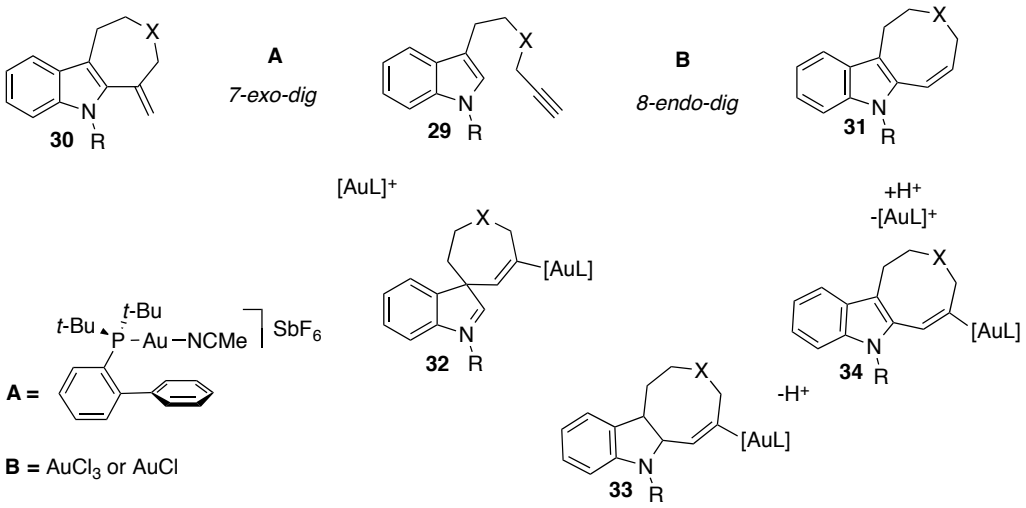
Scheme 4. Outcome of metal-catalyzed diazo decomposition of α-diazocyanides or α-diazocarboxylates **20**.

Based on these precedents, Qin *et al.* developed the second generation asymmetric synthesis of (−)-lundurine A, that relied on a diazo cyclopropanation strategy (Scheme 5).[17] The sequential oxidation, dihydroxylation and oxidative cleavage of previously obtained intermediate **17** provided aldehyde **25** in 27% yield. Condensation of **25** with tosyl hydrazide delivered diazo precursor **26**, which was converted into corresponding hexacycle **28** *via* a one-pot Bamford-Stevens diazotization / diazo decomposition / cyclopropanation cascade employing 50 mol% of $Cu(TBS)_2$.



Scheme 5. Qin's second generation asymmetric synthesis of (−)-lundurine A.

In 2006, our group reported that 8-membered ring formation can be achieved *via* intramolecular hydroarylation of alkynes by indoles in a controlled and efficient manner employing gold catalysis (Scheme 6).[20] Alkynyl indoles can be cyclized in a 7-*exo-dig* or 8-*endo-dig* fashion, depending on the catalyst used. Electron-rich bulky gold complexes favor the formation of 7-membered rings **30** whereas $AuCl_3$ or AuCl led to 8-*endo-dig* products **31**.[20c]



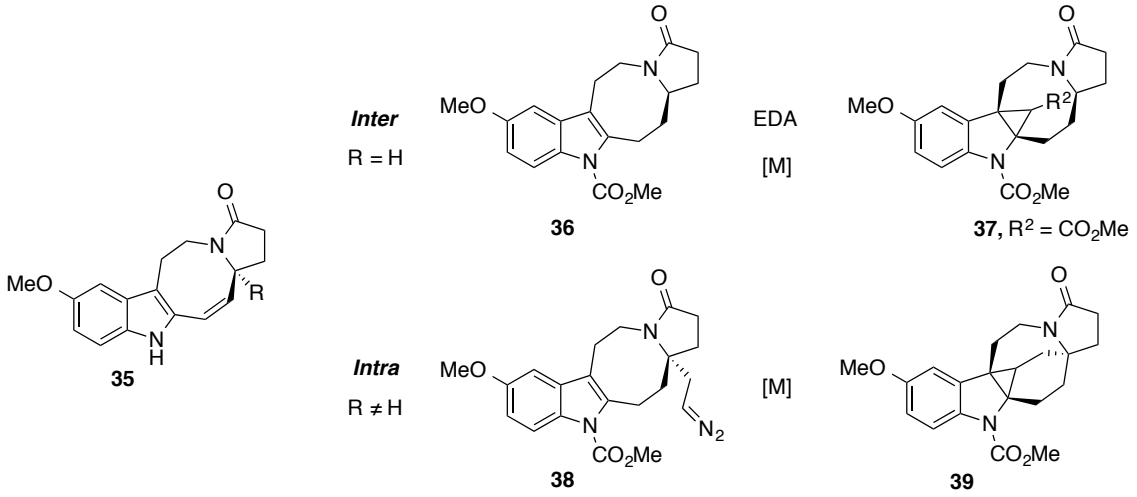
Scheme 6. Hydroarylation of alkynes by indoles employing gold catalysis

Rationalizing the experimental results, our group proposed a possible mechanism for the indoloazocine formation.[20b] The catalytic cycle starts with the activation of alkyne **29** by gold followed by formation of spirocyclic 7-membered ring iminium ion **32** by attack of indole at the C3 position. Spirocyclic **32** then undergoes a 1,2-alkenyl migration to provide the tertiary cation **33**. The aromatization through loss of a proton and protodeauration delivers the desired indoloazocine **31** and completes the catalytic cycle. The 7-*exo-dig* product formation probably proceeds in a similar manner by *6-exo-dig* cyclization at the C3 position of the indole followed by 1,2-alkenyl shift, aromatization, and protodeauration ultimately furnishing the indole **30**.

This transformation could be used as a key synthetic step in the total synthesis of the lundurines. Since the formation of the tetracyclic core of **35** could be easily achieved by the gold-catalyzed hydroarylation of alkynes by indoles, our group proposed two strategies for the total synthesis of the lundurines (Scheme 7).[21] The first approach

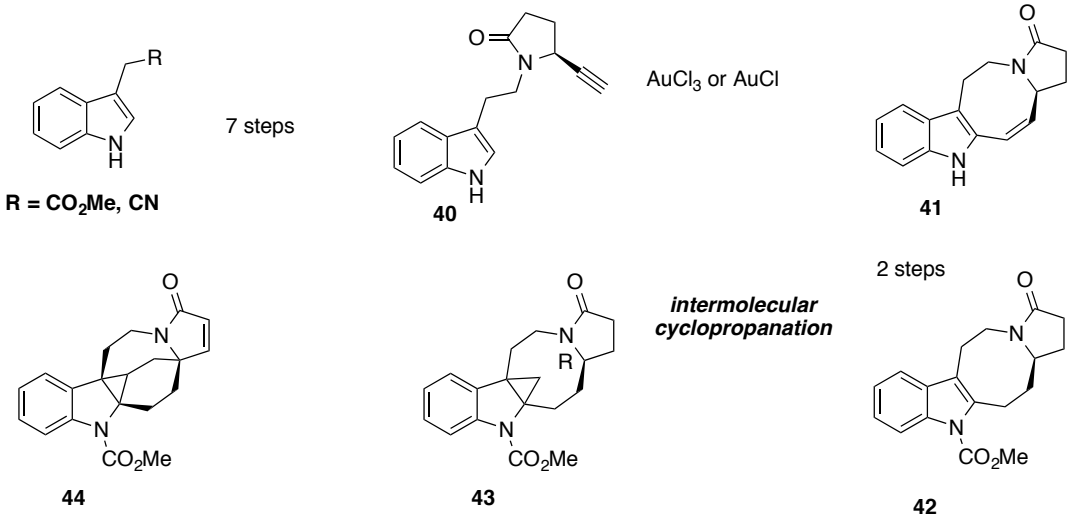
(20) (a) Ferrer, C.; Echavarren, A. M. *Angew. Chem. Int. Ed.* **2006**, *45*, 1105–1109. (b) Ferrer, C.; Amijs, C. H. M.; Echavarren, A. M. *Chem. Eur. J.* **2007**, *13*, 1358–1373. (c) Ferrer, C.; Escribano-Cuesta, A.; Echavarren, A. M. *Tetrahedron* **2009**, *65*, 9015–9020.
(21) Escribano-Cuesta, A. *PhD thesis*, ICIQ, **2012**.

relied on the intermolecular cyclopropanation of indole **36** with ethyl diazoacetate (EDA) followed by the formation of the tetrasubstituted carbon center C20. In the second approach, hexacyclic compound **39** would be obtained from diazoindole **38** *via* an intramolecular cyclopropanation.



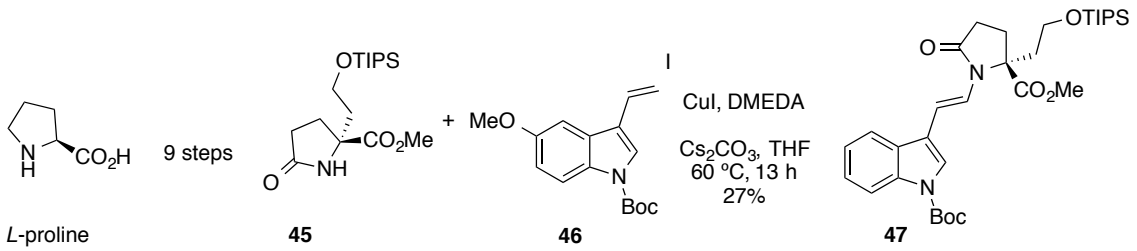
Scheme 7. Inter- and intramolecular strategies for the total synthesis of the lundurines.

The precursor for the gold-catalyzed hydroarylation **40** was obtained in enantiopure form in 7 steps starting from methyl 2-(1*H*-indol-3-yl) acetate (Sheme 8).[20c,21] Gold-catalyzed cyclization followed by protection of indole and hydrogenation delivered tetracycle **42**, which was the desired substrate for intermolecular cyclopropanation. However, the formation of the indolylcyclopropane system catalyzed by several metal complexes failed in all cases. Therefore, this intermolecular approach was abandoned.



Scheme 8. Studies towards the synthesis of the lundurines *via* intermolecular approach.

Advanced intermediate **45,** which would be required for the intramolecular approach, was synthesized from *L*-proline in 9 steps and further subjected to the direct alkylation with 3-(2-bromoethyl)-1*H*-indole to furnish the desired lactam in 23% yield.[21] In addition, the copper mediated coupling of indolylvinyliodide **46** and lactam **45** led to the desired alkenylindole **47** only in low yield (Scheme 9).



Scheme 9. Synthesis of chiral alkynyl precursor **47**.

The gold(I)-catalyzed intramolecular hydroarylation of alkynes by indoles remained a promising strategy for the synthesis of lundurines A–C. However, the synthesis of a suitable cyclization precursor still required extensive development to further explore this approach.

Objectives

Recently the total synthesis of lundurines A and B have been reported.[13-17] However, all previous approaches to this family of molecules were lengthy, involving at least twenty linear synthetic steps, and are unsuitable for analog synthesis.

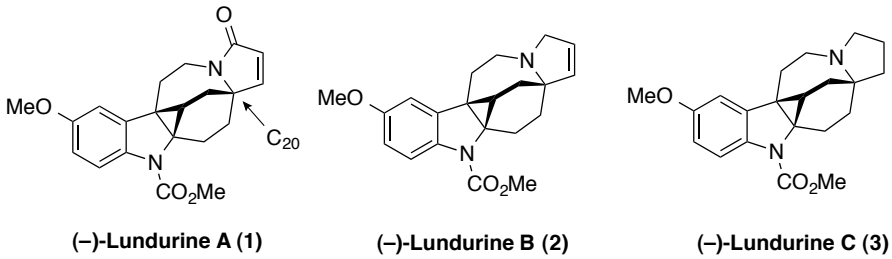
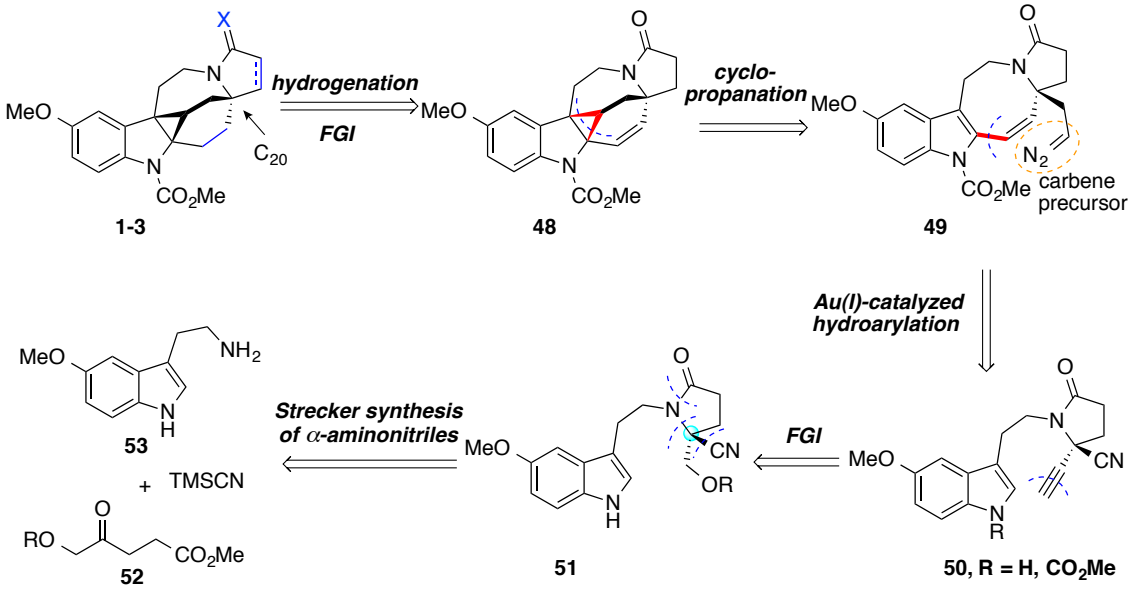


Figure 3. Lundurines A−C.

We focused our attention on three members of the *Kopsia* alkaloids family, lundurines A−C, as part of our investigation on the application of gold catalysis for the synthesis of architecturally challenging natural products. We redesigned our retrosynthetic approach as presented in Scheme 10.



Scheme 10. Retrosynthetic approach towards lundurines A−C.

We envisioned that lundurines A–C could be synthesized by late stage functionalization of hexacycle **48** which should be easily accessible *via* the transition metal-catalyzed cyclopropanation of a carbene precursor **49**. The main tetracyclic core of the molecule could be constructed by a gold(I)-catalyzed intramolecular hydroarylation of alkyne **50**.

As was previously demonstrated by our group, this reaction proceeds with high *endo* selectivity and in high yield to form the pyrroloazocine ring system. The alkyne precursors for the hydroarylation could be obtained by simple functional group manipulation of key intermediate **51.** We decided to generate the tetrasubstituted carbon center C20 in a single step very early in the synthesis using Strecker synthesis of α-aminonitriles. Thus, we envisioned a 3-component condensation of commercially available tryptamine, easily accessible oxoester **52** and cyanide anion, with the latter as the *C*-nucleophile. This tandem transformation consists of the condensation between the primary amine and ketone then addition of cyanide to the *in situ* formed iminium cation followed by lactamization, ultimately generating the desired α-amidonitrile and significantly increasing molecular complexity. The application of an asymmetric version of the Strecker synthesis of α-aminonitriles would set the stage for the enantioselective synthesis of lundurines A–C.

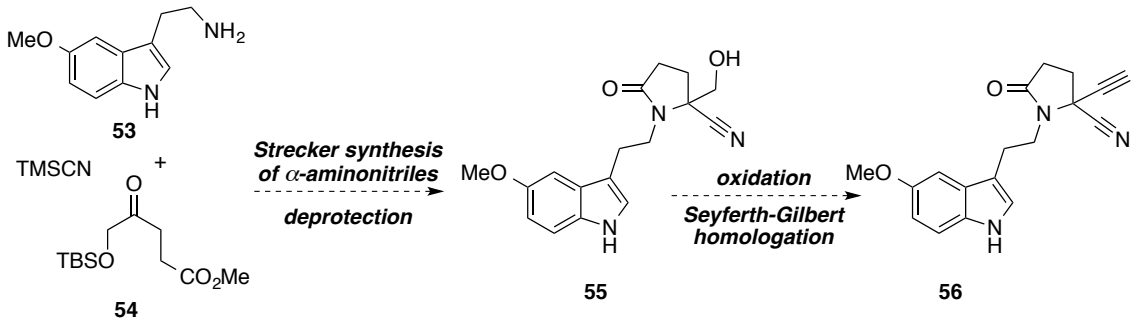
In summary, the objectives of this project are:

1. The generation of the C20 stereocenter *via* Strecker reaction or alternative methods.
2. The polyhydroazocine ring formation using the gold(I)-catalyzed intramolecular hydroarylation of alkynes.
3. The development of an efficient method for the intramolecular cyclopropanation of indoles.
4. The completion of both the synthesis of racemic lundurines and the development of an enantioselective total syntheses of these natural products.

Results and discussion[22]

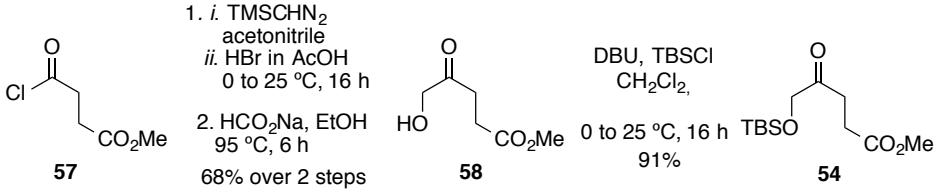
Studies towards the synthesis of lundurines A–C via Strecker reaction

As was previously mentioned, the synthesis of the lundurine skeleton requires the development of an efficient method to generate the required C20 stereocenter, the polyhydroazocine ring construction and the intramolecular cyclopropanation of indoles. We started the elaboration of the synthesis of an alkyne precursor for the gold-catalyzed hydroarylation, aiming at establishing the C20 stereocenter very early in the synthetic sequence. Our first approach relied on a one-pot formation of an α-amidonitrile *via* Strecker reaction.[23] The deprotection of the primary silyl ether followed by oxidation and Seyferth-Gilbert[24] homologation using Ohira-Bestmann reagent would deliver the desired alkynylindol **56** (Scheme 11).



Scheme 11. Proposed synthesis of an alkynylindole **56**.

We synthesized hydroxyketone **58** according to the previously reported procedure[25] and protected the primary alcohol as a silyl ether to provide the ketone partner **54** required for the Strecker reaction (Scheme 12).

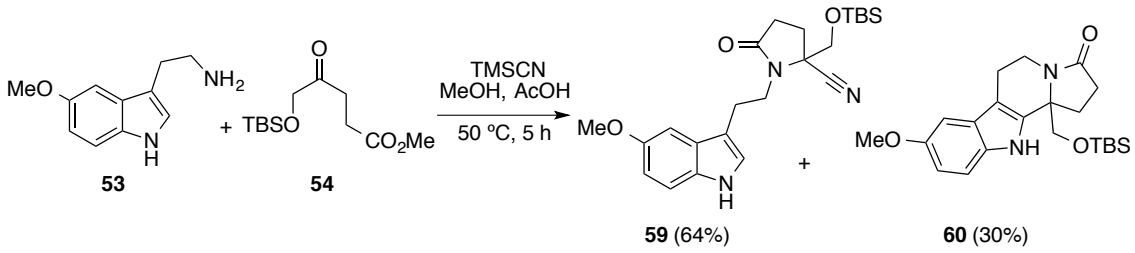


Scheme 12. Synthesis of oxoester **54**.

(22) I would like to thank Dr. Michael E. Muratore for his contribution in developing the strategy towards the enantioselective syntheses of lundurines A−C and Ruth Dorel for the DFT calculations and additional experimental help.

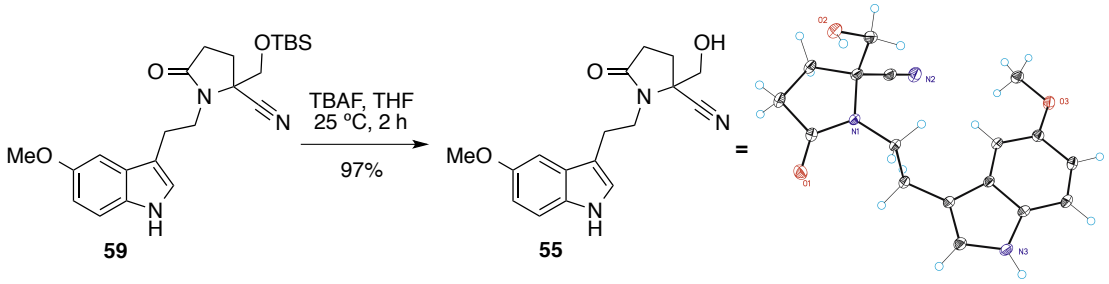
(23) Wang, J.; Liu, X.; Feng, X. *Chem. Rev*. **2011**, *111*, 6947−6983.
(24) Müller, S.; Liepold, B.; Roth, G. J.; Bestmann, H. J. *Synlett*, **1996**, 521−522.
(25) Tang, G.; Tian, H.; Ma, D. *Tetrahedron* **2004**, *60*, 10547–10552.

The condensation of commercially available 5-methoxytryptamine **53** with ketoester **54** under acidic conditions, addition of cyanide to iminium cation, followed by lactamization gave α-amidonitrile **59** in 64% yield along with the product of Pictet-Spengler type reaction **60**[26] (Scheme 13).



Scheme 13. Strecker reaction.

The deprotection of silyl ether **59** with TBAF proceeded smoothly and delivered primary alcohol **55**, its structure was confirmed by single crystal X-ray diffraction (Scheme 14).

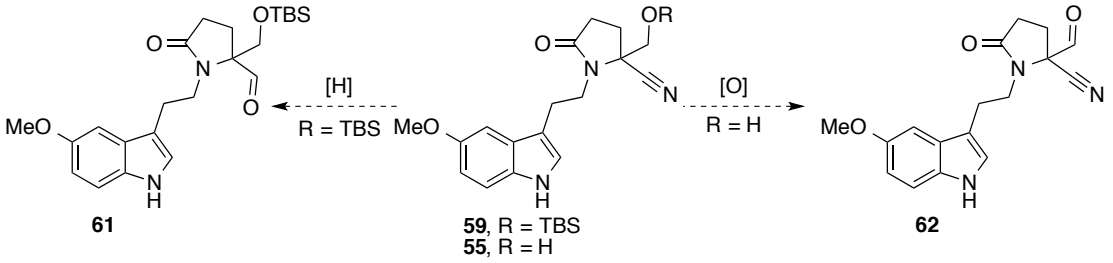


Scheme 14. Formation of primary alcohol **55**. ORTEP representation of the X-ray crystal structure of **55**. 50% probability of the thermal ellipsoids.

The oxidation of the primary alcohol **55** was found to be problematic. All conditions tested such as Dess-Martin,[27] Swern,[28] Ley-Griffith,[29] Parikh-Doering,[30] PCC,[31] IBX[32] and other procedures failed to provide aldehyde **62** (Scheme 15). Either no reactivity or

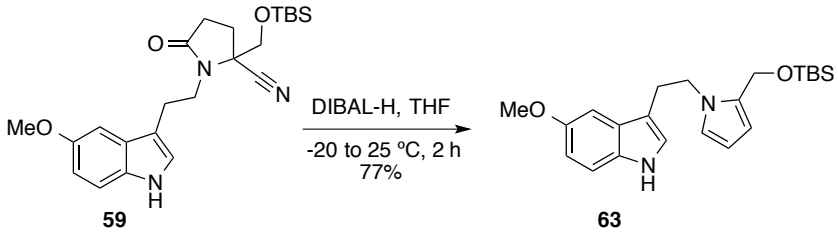
(26) (a) Muratore, M. E.; Holloway, C. A.; Pilling, A. W.; Storer, R. I.; Trevitt, G.; Dixon, D. J. *J. Am. Chem. Soc.* **2009**, *131*, 10796–10797. (b) Holloway, C. A.; Muratore, M. E.; Storer, R. I.; Dixon, D. J. *Org. Lett.* **2010**, *12*, 4720–4723.
(27) Dess, D. B.; Martin, J. C. *J. Org. Chem.* **1983**, *48*, 4155–4156.
(28) (a) Omura, K.; Sharma, A. K.; Swern, D. *J. Org. Chem.* **1976**, *41*, 957–962. (b) Huang, S. L.; Omura, K.; Swern, D. *Synthesis* **1978**, 297–299.
(29) Griffith, W. P; Ley, S. V.; Whitcombe, G. P.; White, A. D. *J. Chem. Soc., Chem. Commun.* **1987**, 1625−1627.
(30) Parikh, J. R.; Doering, W. v. E. *J. Am. Chem. Soc.*, **1967**, *89,* 5505–5507.
(31) Corey, E. J.; Suggs, J. W. *Tetrahedron Lett.,* **1975**, *16*, 2647−2650.
(32) More, J. D.; Finney, N. S. *Org. Lett*. **2002**, *17*, 3001−3003.

decomposition of the starting material were observed. The decomposition of **55** can be explained by the presence of an unprotected electron-rich indole system in the molecule. These results forced us to revise our strategy and use the nitrile moiety as the alkyne precursor instead.



Scheme 15. Oxidation and reduction strategy.

The attempt of reduction with Raney nickel / formic acid provided an unidentified complex mixture along with recovered starting material. Reaction of **59** with catecholalane or DIBAL−H resulted in the formation of undesired substituted pyrrole **63** (Scheme 16).



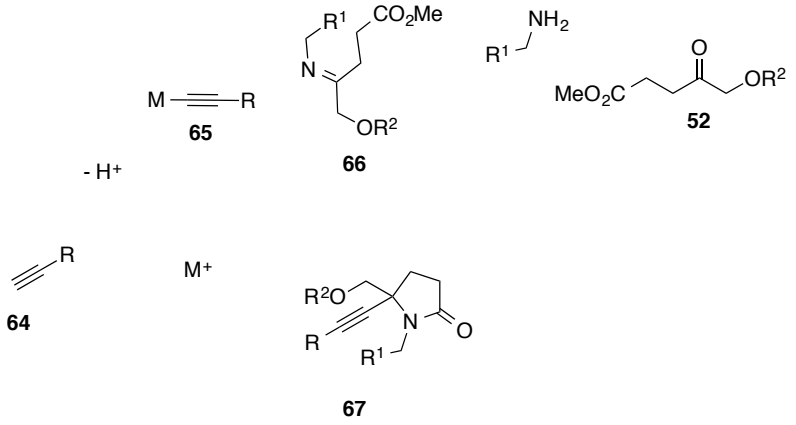
Scheme 16. Nitrile reduction with DIBAL−H.

Although the further investigation of functional group modification methods was considered, we decided to refocus our efforts on alternative strategies employing different *C*-nucleophiles in order to generate the fully substituted carbon center C20.

Studies towards the synthesis of lundurines A–C via KA² reaction

Since the functional group modification of cyanolactam **59** was problematic, we decided to investigate the formation of the fully substituted carbon center from the direct condensation of a ketone, an amine and an alkyne (hereinafter the abbreviation KA^2 will refer to this type of reaction).[33] We envisioned the synthesis of lactams bearing an alkyne moiety by the 3-component coupling of commercially available tryptamine **53**, various oxoesters of type **52** and acetylides, the latter as the *C*-nucleophile. This transformation would provide the access to a precursor for the planned gold-catalyzed hydroarylation.

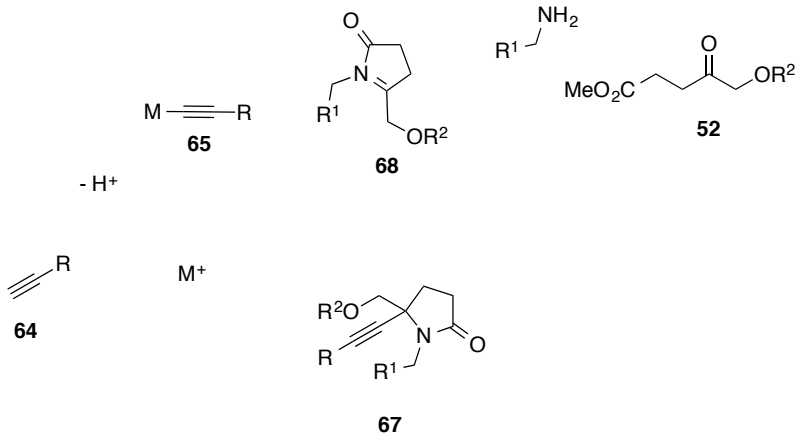
There are two possible mechanisms that can be proposed for this transformation. The metal catalyst could react with the alkyne **64** to form a metal acetylide **65,** while the condensation of the primary amine with the ketone **52** delivers the imine **66**. Nucleophilic addition of the acetylide **65** to the iminium carbon of **66** followed by lactamization would provide the alkynyl lactam **67** and regenerate the metal catalyst (Scheme 17).



Scheme 17. First proposed mechanism for KA^2 reaction

Alternatively, the lactamization might occur before the addition of nucleophile to form an *N*-acyl iminium ion **68**, which may undergo the attack by the metal acetylide **65** (Scheme 18).

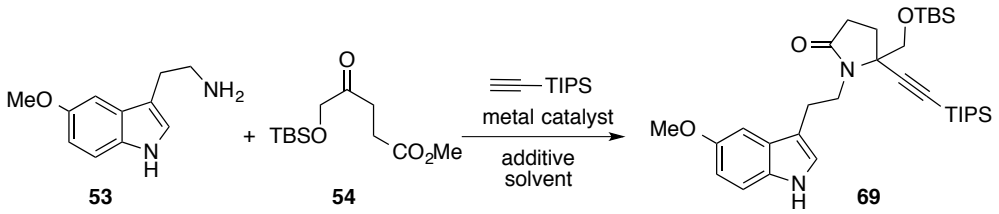
(33) (a) Pierce, C. J.; Nguyen, M.; Larsen, C. H. *Angew. Chem. Int. Ed*. **2012**, *51*, 12289–12292. (b) Pereshivko, O. P.; Peshkov, V. A.; Van der Eycken, E. V. *Org. Lett*. **2010**, *12*, 2638–2641. (c) Tang, X.; Kuang, J.; Ma, S. *Chem. Commun*. **2013**, *49*, 8976−8978. (d) Pierce, C. J.; Larsen, C. H. *Green Chem.* **2012**, *14*, 2672–2676. (e) Cheng, M.; Zhang, Q.; Hu, X.-Y.; Li, B.-G.; Ji, J.-X.; Chan, A. S. C. *Adv. Synth. Catal*. **2011**, *353*, 1274–1278.



Scheme 18. Second proposed mechanism for KA^2 reaction

Taking both scenarios into consideration, we performed initial experiments with the previously synthesized oxoester **54**, 5-methoxytryptamine and triisopropylsilyl acetylene, employing different conditions for the KA^2 reactions.[33] Varying the catalysts, catalyst loadings, solvents, additives and temperatures, we found that in most of the cases the Pictet-Spengler type product **60** was exclusively formed and only trace amounts of the alkynyl indole **69** were observed (Table 1). The desired product **69** of the KA^2 reaction was obtained in moderate yield only when we employed a stoichiometric amount of copper(I) chloride and 25 mol% of cesium carbonate under solvent free conditions (Table 1, entry 5).

Table 1. Study of the KA^2 reaction conditions.



Entry	Metal catalyst	Additive	Solvent	Temperature, °C	Yield, %[a]
1	CuCl (100 mol%)	−	water	100	ND
2	CuBr (100 mol%)	4 Å MS	DMF	100	traces[b]
3	CuBr (10 mol%)	4 Å MS	toluene	100	traces[b]
4	CuBr (100 mol%)	−	−	100	ND[b]
5	CuCl (100 mol%)	Cs_2CO_3 (25 mol%)	−	110	55
6	CuCl (10 mol%)	Cs_2CO_3 (25 mol%)	toluene	110	ND[b]
7	CuCl (10 mol%)	Cs_2CO_3 (100 mol%)	−	110	26
8	CuCl (10 mol%)	$Ti(OEt)_4$ (50 mol%)	toluene	110	ND[b]
9	$CuCl_2$ (25 mol%)	−	toluene	110	ND[b]
10	CuI (20 mol%)	$Ti(OEt)_4$ (25 mol%)	−	100[c]	traces[b]
11	$AuBr_3$ (5 mol%)	$Ti(OEt)_4$ (50 mol%)	−	110	ND[b]

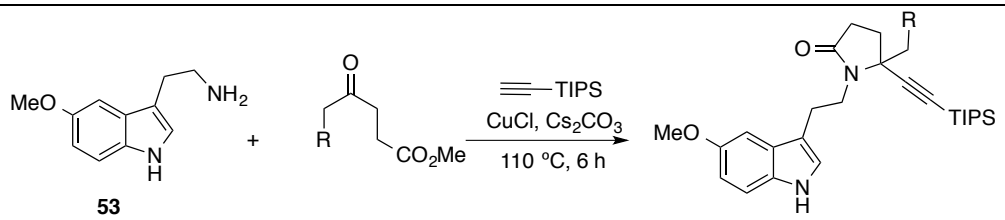
Note: all reactions performed on a 0.1 mmol scale, tryptamine/ketone/alkyne 1 : 1 : 2 ratio. [a] Isolated yield. [b] Product of Pictet-Spengler type reaction **60** isolated only. [c] reaction performed in MW.

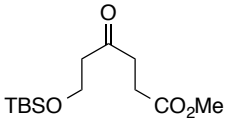
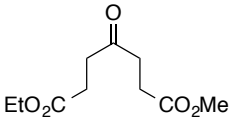
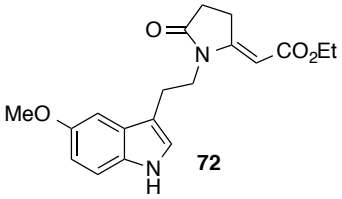
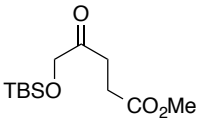
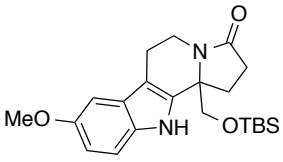
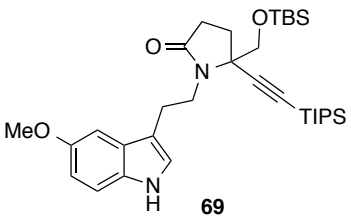
Based on these preliminary results we concentrated our attention on possible ketone partners for the KA^2 reaction. We synthesized oxoesters **70**[34] and **71**[35] according to the reported procedures and subjected them to our previously optimized conditions. Oxoester

(34) Campbell, E. L.; Zuhl, A. M.; Liu, C. M.; Boger, D. L. *J. Am. Chem. Soc.* **2010**, *132*, 3009–3012.
(35) Nudelman, A.; Nudelman, A. *Synthesis* **1999**, *4*, 568–570.

70 remained intact and could be fully recovered. This can be explained by the low reactivity of the acyclic unactivated ketones towards primary amines in comparison to cyclic or α-hydroxyketones.[36] In the case of ketodiester **71**, undesired pyrrolidinone **72** was formed in 79% yield (Table 2), its structure was confirmed by single crystal X-ray diffraction.

Table 2. Studies of possible ketone partners for KA^2 reaction.



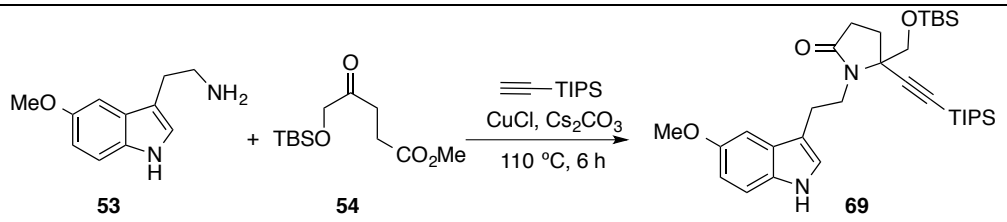
Entry	Ketone	Obtained product	Yield, %[a]
1	 **70**	No reaction	–
2	 **71**	 **72**	79
3	 **54**	 **60**	55
		 **69**	32

Note: all reactions performed on a 0.1 mmol scale with 100 mol% of CuCl under solvent free conditions, tryptamine/ketone/alkyne 1 : 1 : 2 ratio. [a] Isolated yield.

(36) Anslyn, E. V.; Dougherty, D. A. *Modern Physical Organic Chemistry*, University Science Books, Sausalito, CA, **2006**, 562.

Since only oxoester **54** delivered the desired alkynyl pyrrolidinone **69**, we focused on studying the effect of the scale on the outcome of the reaction (Table 3). The heterogeneous nature of the system and the difficulty of evenly heating the reaction medium at the required high temperature, resulted in the dramatic decrease of the yield when the reaction was carried out on a 5 mmol scale. On a 10 mmol scale, the Pictet-Spengler type reaction was predominant and only 10% yield of the KA^2 coupling product could be isolated.

Table 3. Studies of effect of the scale on the outcome of the KA^2 reaction.



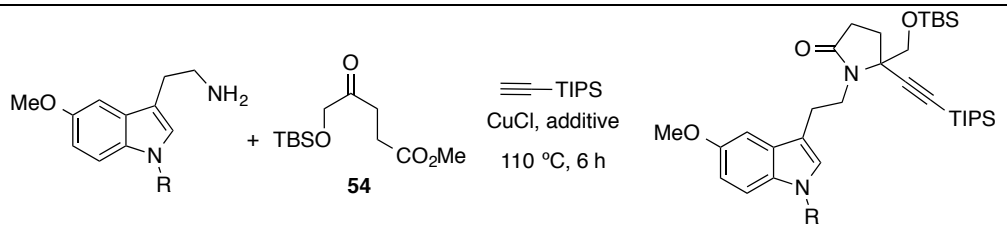
53 **54** **69**

Entry	Scale, mmol	Yield % [a]
1	0.1	55
2	5	32
3	10	10

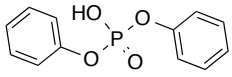
Note: all reactions performed with 100 mol% of CuCl under solvent free conditions, tryptamine/ketone/alkyne 1 : 1 : 2 ratio. [a] Isolated yield.

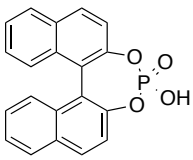
These results prompted us to reinvestigate and optimize the reaction conditions. Changing the basic additive to different acids led to the reduction of the yield in the case of diaryl and BINOL phosphoric acids **A** and **B** (Table 4). On the other hand, the use of 10 mol % of MacMillan TiPSY catalyst **C** provided the desired alkynyl pyrrolidinone **69** in 68% yield. Decreasing the additive loading to 5 mol % did not affect the outcome of the reaction, however a further decrease to 2.5 mol % had a detrimental effect. Placing an electron-withdrawing group on the indole nitrogen to reduce the nucleophilicity of indole and suppress the Pictet-Spengler type reaction did not lead to any improvement.

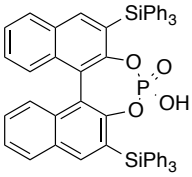
Table 4. Investigation of additive effect on the outcome of the KA^2 reaction.



Entry	R	Additive	mol%	Yield, %[a]
1	H	Cs_2CO_3	25	55
2	H	**A**	20	15
3	H	**A**	10	50
4	H	**A**	5	48
5	H	**A**	2.5	30
6	H	**B**	5	46
7	H	**C**	10	68
8	H	**C**	5	67
9	H	**C**	2.5	54
10	Ts[b]	Cs_2CO_3	25	29
11	Ts[b]	**A**	5	30
12	Ts[b]	**B**	5	37
13	Ts[b]	**C**	5	46

A = 

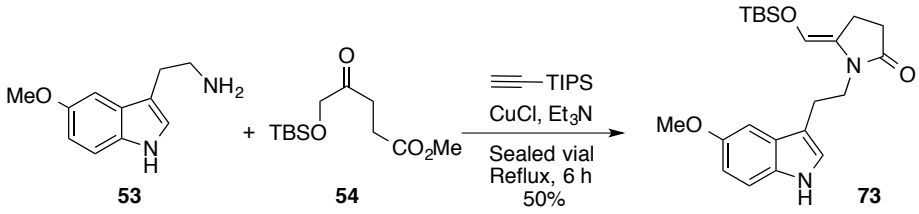
B = 

C = 

Note: all reactions performed on a 0.1 mmol scale with 100 mol% of CuCl under solvent free conditions, tryptamine/ketone/alkyne 1 : 1 : 2 ratio. [a] Isolated yield. [b] Prepared according to a reported procedure.[37]

(37) Russell, M. G. N.; Baker, R. J. B.; Barden, L.; Beer, M. S.; Bristow, L.; Broughton, H. B.; Knowles, M.; McAllister, G.; Pater, S.; Castro, J. L. *J. Med. Chem*. **2001**, *44*, 3881 – 3895.

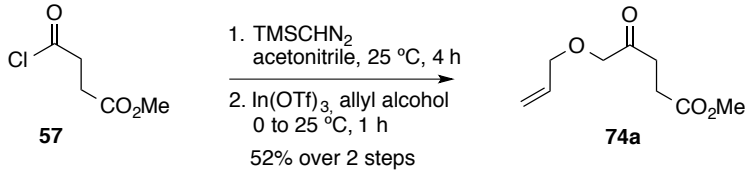
We decided to perform the reaction in a basic medium since scaling up under solvent-free conditions remained problematic and large amounts of the corresponding tetrahydro-β-carbolines were obtained in the presence of Brønsted or Lewis acids. To circumvent these problems, we chose Et_3N as a solvent. To our surprise, we obtained silyl vinyl ether **73** in 50 % yield (Scheme 19). The ready access to this type of pyrrolidinones led us to consider exploring another strategy consisting in the introduction of an allyl moiety, which would act as an intramolecular *C*-nucleophile *via* Claisen rearrangement.



Scheme 19. Synthesis of silyl vinyl ether **73**.

Our new proposal was to condense oxoester **74a** with commercially available 5-methoxytryptamine. This should provide an imine, which after lactamization / Claisen rearrangement[38] sequence would generate the fully substituted carbon center C20 bearing an aldehyde moiety that is perfectly suited for a Seyferth-Gilbert homologation.

We developed a procedure for the multi-gram synthesis of oxoester **74a** from commercially available acyl chloride **57** and TMS diazomethane. The corresponding diazo compound was further subjected to decomposition in the presence of $In(OTf)_3$ in allyl alcohol as a solvent to provide the desired oxoester **74a** in 52% yield over 2 steps (Scheme 20).

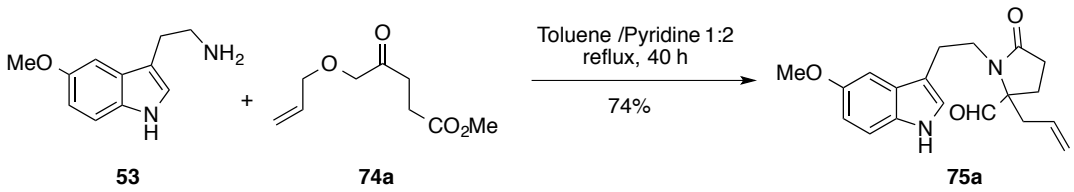


Scheme 20. Synthesis of oxoester **74a**.

To our delight, the complex tandem condensation / lactamization / [3,3]-sigmatropic Claisen rearrangement proceeded well providing the aldehyde **75a** in a mixture with its

(38) (a) Barluenga, J.; Aznar, F.; Liz, R.; Bayod, M. *J. Chem. Soc., Chem. Commun.* **1984**, 1427–1428. (b) Desmaële, D.; Champion, N. *Tetrahedron Lett.* **1992**, *33*, 4447–4450. (c) Deyine, A.; Poirier, J.-M.; Duhamel, P. *Synlett* **2008**, 260–262.

Schiff base. Mild acidic aqueous work-up furnished the desired product in 74% yield (Scheme 21).



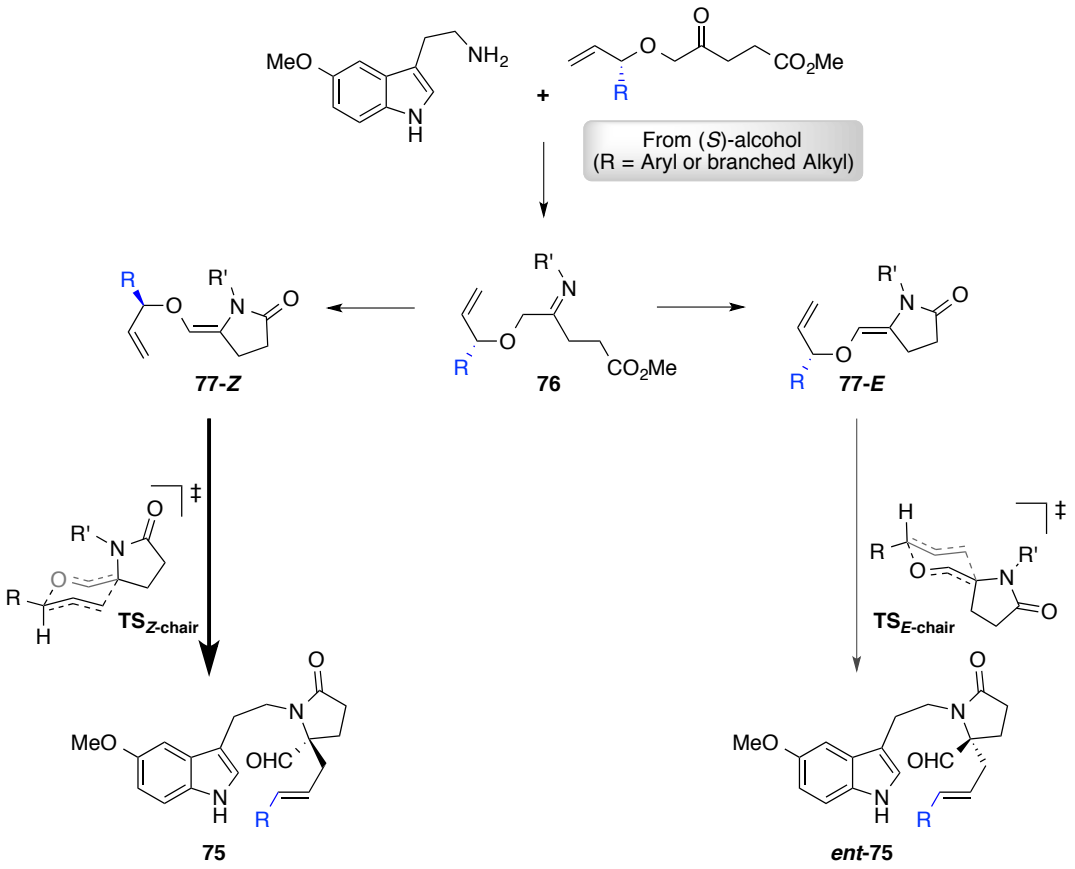
53 **74a** **75a**

Scheme 21. Tandem condensation / lactamization / Claisen rearrangement.

Having developed an efficient method for the synthesis of the alkyne precursor for gold-catalyzed hydroarylation in racemic form, we focused our investigation on its asymmetric variant. These results will be discussed in detail in the following section.

Study on the tandem condensation / lactamization / [3,3]-sigmatropic Claisen rearrangement

Based on the results discussed in the previous section, we elaborated our new strategy for the asymmetric synthesis of aldehyde **75**. For the synthesis of key chiral intermediate **75**, we envisioned the condensation of enantiopure oxoester **74** with commercially available 5-methoxytryptamine. Under dehydrative conditions, this should lead to imine **76**, which should undergo lactamization with the methyl ester to form pyrrolidinones **77-*Z*** and **77-*E***. Ultimately, **77-*Z*** and **77-*E*** could afford 7**5** through a Claisen rearrangement. In order to synthesize the alkyne precursor for the gold(I)-catalyzed hydroarylation in enantioenriched form, we proposed to enantioselectively build the C20 stereocenter, by enantiodiscrimination during the course of the Claisen rearrangement,[38] through transfer of chirality (Scheme 22). Our proposed transfer of chirality relied on the hypothesis that the [3,3]-sigmatropic rearrangement should proceed *via* the less energetically demanding transition states with the R group placed in a pseudo-equatorial position (Scheme 2).

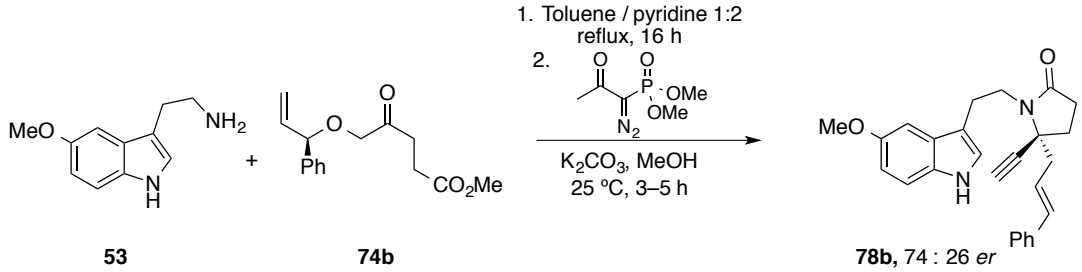


Scheme 22. Initial proposal for the enantioselective Claisen rearrangement.

Although there is a profusion of studies on enantioselective Claisen rearrangement catalyzed by chiral transition-metal complexes,[39] examples of the efficient transfer of chirality in flexible systems featuring a "traceless" chiral auxiliary on the allyl fragment and in the absence of Lewis acid are scarce. [40]

It is important to remind that the use of basic conditions in this transformation is essential in order to avoid the Pictet-Spengler type reaction that would form the corresponding tetrahydro-β-carbolines.[26] A 2 : 1 mixture of pyridine / toluene proved to be efficient in the case of allyl oxoester **74a**, affording high yields of lactam **75a**. Thus, it was selected as a starting point for the investigation of the asymmetric synthesis of chiral aldehyde **75b**. Commercially available (*R*)-1-phenylprop-2-en-1-ol **79b** was chosen as a precursor for our model system and could be converted into the required chiral oxoester **74b** in a single step following the procedure for the preparation of **74a** mentioned above.

As expected, the designed transformation proceeded smoothly and the desired product **75b** was isolated in 61% yield (Scheme 23). The aldehyde **75b** proved to be unstable on HPLC and the enantiomeric excess determination at that stage was not feasible. However, the homologation with Ohira-Bestmann reagent delivered the enantioenriched stable alkyne **78b** with 74 : 26 *er*.



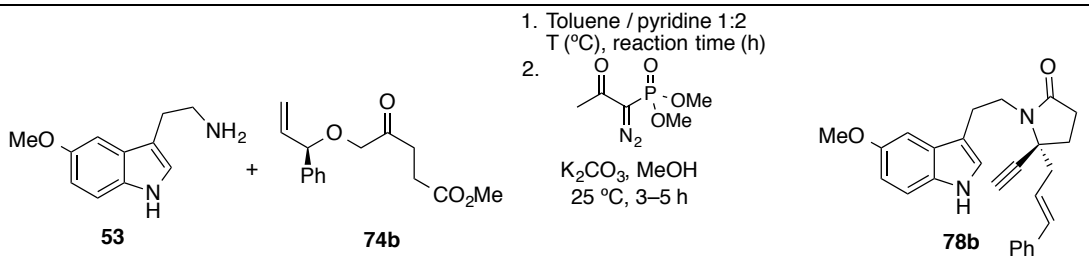
53 **74b** **78b,** 74 : 26 *er*

Scheme 23. Enantioselective Claisen rearrangement.

We were pleased to find that the transfer of chirality in our flexible model system was successful. However, its moderate efficiency forced us to continue our investigation. Lowering the temperature did not affect the enantiomeric ratio of the product formed but rather prolonged the reaction times were required to achieve acceptable conversions (Table 5).

(39) Martín Castro, A. M. *Chem. Rev.* **2004***, 104*, 2939–3002.
(40) (a) Pandey, G.; Khamrai, J.; Mishra, A. *Org. Lett.* **2015**, *17*, 952–955. (b) Zhang, Q.-Q.; Xie, J.-H.; Yang, X.-H.; Xie, J.-B.; Zhou, Q.-L. *Org. Lett.* **2012**, *14*, 6158–6161. (c) Güneş, Y.; Polat, M. F.; Sahin, E.; Fleming, F. F.; Altundas, R. *J. Org. Chem.* **2010**, *75*, 7092–7098.

Table 5. Investigation of temperature influence on the efficiency of transfer of chirality

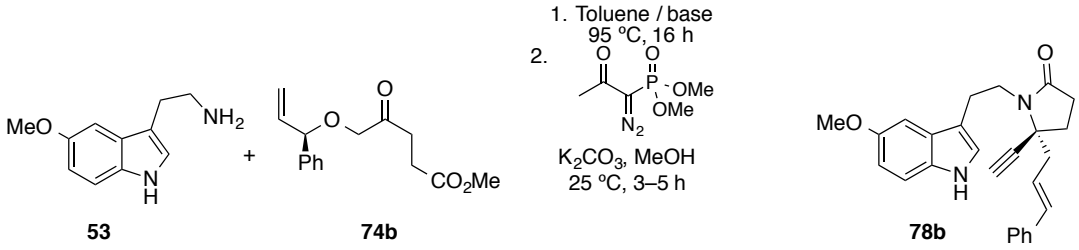


Entry	Temperature, °C	Time, h	*er*[a]
1	130	3	74 : 26
2	95	8	73 : 27
3	65	20	74 : 26
4	30	40[b]	75 : 25

Note: all reactions performed on a 0.05 mmol scale in a sealed MW vial. [a] *er* measured on alkyne **78b** using chiral HPLC, IA column. [b] Low conversion of starting material.

A variety of organic bases was tested as a co-solvent for the double condensation / Claisen rearrangement (Table 6). When the reaction was performed in a mixture of toluene and pyridine, 2,4,6-collidine, TMEDA or cyclohexyldimethylamine, a similar efficiency in the transfer of chirality was observed. Using Hünig's base, triethylamine or 1,2,2,6,6-pentamethylpiperidine (PMP) led to the formation of the product **78b** with nearly 80 : 20 *er*. Although employing 200 mol % of proton sponge as the base provided the product with the same *er*, the poor solubility of both starting material and product made the use of these conditions impractical. In the case of DBU as the base, no reaction took place. Rationalizing these observations, we can conclude that the efficiency of transfer of chirality strongly depends on the combination of basicity and bulkiness of the base used. We selected triethylamine and PMP for further investigation.

Table 6. Investigation of base influence on the efficiency of transfer of chirality.

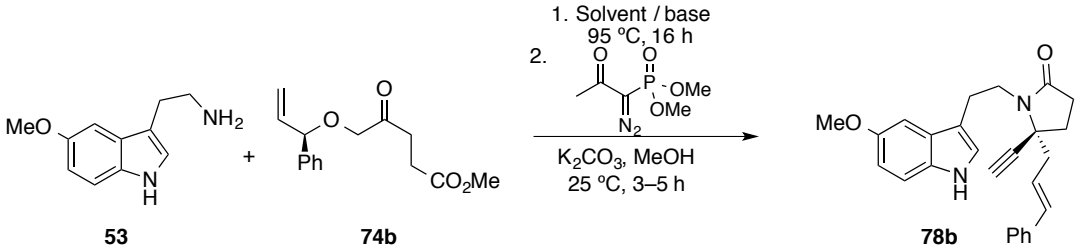


Entry	Solvent	*er*[a]	*p*K_a[b]
1	Pyridine : toluene (2 : 1)	73 : 27	5.25
2	2,4,6-collidine : toluene (2 : 1)	74 : 26	7.41
3	TMEDA : toluene (2 : 1)	73 : 27	8.97
4	$CyNMe_2$: toluene (2 : 1)	71 : 29	10.00
5	Hünig's base : toluene (2 : 1)	79 : 21	10.30
6	Et_3N : toluene (2 : 1)	80 : 20	10.75
7	PMP : toluene (2 : 1)	80 : 20	11.25
8	Proton sponge : toluene [c]	80 : 20[d]	12.10
9	DBU[e]: toluene	–[f]	13.50

Note: all reactions performed on a 0.05 mmol scale in a sealed MW vial. [a] *er* measured on alkyne using chiral **78b** HPLC, IA column. [b] *p*K_a in water. [c] 200 mol% of proton sponge. [d] Low conversion due to the poor solubility of starting material. [e] 500 mol% of DBU. [f] No reaction. TMEDA − tetramethylethylenediamine, PMP – 1,2,2,6,6-pentamethylpiperidine, DBU − 1,8-diazabicyclo[5.4.0]undec-7-ene.

Further optimization was performed to study the effect of different solvents on the reaction outcome (Table 7). When the reaction was carried out in a mixture of triethylamine and a polar solvent such as THF, dioxane or acetonitrile, a reduction of enantioslectivity was observed in comparison with the Et_3N – toluene system. When PMP was used as the base, the nature of the co-solvent barely had any influence on the enantiomeric ratios observed (*ca* 80 : 20 *er*).

Table 7. Investigation of solvent influence on the efficiency of transfer of chirality.



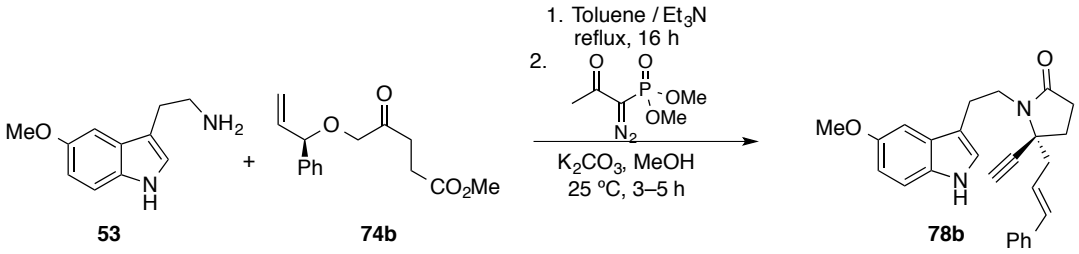
53 **74b** **78b**

Entry	Solvent	Temperature, °C	*er*[a]
1	Et_3N : toluene (2 : 1)	95	80 : 20
2	Et_3N : THF (2 : 1)	95	75 : 25
3	Et_3N : dioxane (2 : 1)	95	77 : 23
4	Et_3N : acetonitrile (2 : 1)	95	73 : 23
5	PMP : toluene (2 : 1)	95	80 : 20
6	PMP : THF (2 : 1)	95	78 : 22
7	PMP : dioxane (2 : 1)	95	80 : 20
8	PMP : acetonitrile (2 : 1)	95	80 : 20

Note: all reactions performed on a 0.05 mmol scale in a sealed MW vial. PMP – 1,2,2,6,6-pentamethylpiperidine. [a] *er* measured on alkyne **78b** using chiral HPLC, IA column.

Since no improvement was observed for the PMP system, we selected triethylamine as the co-solvent, based on practical and economical reasons, and continued our investigation varying the ratio between solvent and base (Table 8). Triethylamine solely as the solvent (no co-solvent) showed to be less efficient and delivered product **78b** with 74 : 26 *er*, while no significant difference in enantiomeric ratio was observed when different ratios of Et_3N – toluene were used. The poor solubility of 5-methoxytryptamine in toluene prompted us to opt for Et_3N − toluene in a 2 : 1 ratio as the optimal solvent system for this transformation.

Table 8. Investigation of solvent-base ratio effect on the efficiency of transfer of chirality.



Entry	Solvent	Temperature, °C	*er*[a]
1	TEA	95	74 : 26
2	TEA : toluene (2 : 1)	95	80 : 20
3	TEA : toluene (1 : 2)	95	77 : 23
4	TEA : toluene (1 : 5)	95	78 : 22
5	TEA : toluene (1 : 10)	95	80 : 20

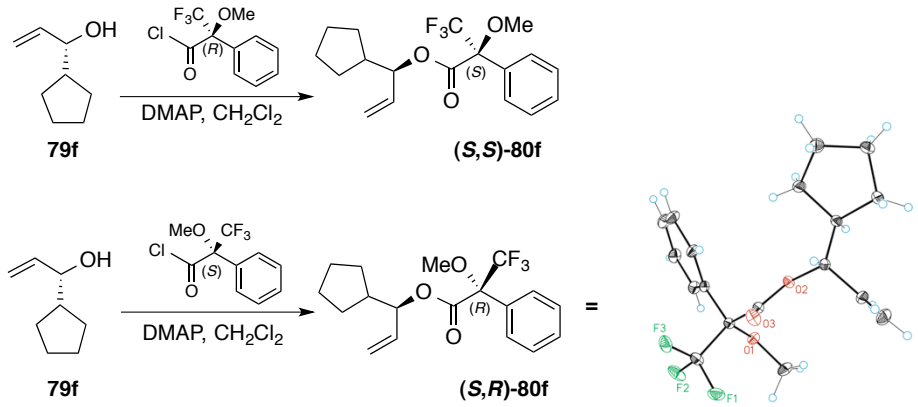
Note: all reactions performed on a 0.05 mmol scale in a sealed MW vial. [a] *er* measured on alkyne **78b** using chiral HPLC, IA column.

With optimal conditions in hand, we started investigating how different chiral auxiliaries can affect the efficiency of the chirality transfer over the course of the double condensation / Claisen rearrangement. We prepared a range of (*S*)-configured chiral alcohols (*S*)-**79c-j** by enzymatic resolution of the racemic allylic alcohols.[41] The enantiopurity of the chiral alcohols bearing alkyl substituents was determined on their dihydrocinnamic ester derivatives.

To confirm the absolute configuration of the chiral alcohols obtained after enzymatic resolution, both (*R*)- and (*S*)-Mosher ester derivatives of (*S*)-**79f** were prepared according to the literature (Scheme 24).[42] (*S*,*R*)-**80f** showed shielding of the cyclopentyl C***H*** and unshielding of the vinyl C***H*** compared to (*S*,*S*)-**80f**, this is consistent with the *S*

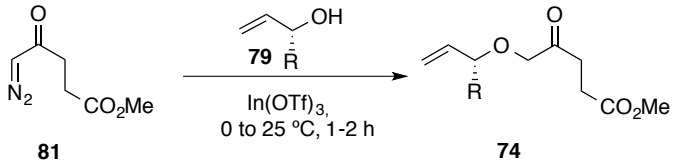
(41) Štambaský, J.; Malkov, A. V.; Kočovský, P. *J. Org. Chem.* **2008**, *73*, 9148–9150.
(42) Wada, R.; Shibuguchi, T.; Makino, S.; Oisaki, K.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* **2006**, *128*, 7687–7691.

configuration of the alcohol.[43] In addition, the absolute configuration of (*S*,*R*)-**80f** was confirmed by single crystal X-ray diffraction.



Scheme 24. Confirmation of the absolute configuration of **79f**. ORTEP representation of the X-ray crystal structure of (*S*,*R*)-**80f**. 50% probability of the thermal ellipsoids.

The alcohols **79c-j** were converted into the corresponding chiral oxoesters **74c-j** in a single step by reaction with diazo compound **81** in the presence of indium(III) triflate (Scheme 25).



Scheme 25. Synthesis of chiral oxoesters **74c-j**.

The enantiopurity of the oxoesters delivered from the chiral alcohols **74c-f** bearing alkyl substituents could not be measured easily by HPLC since they presented no chromophore. However, by analogy with derivatives **74g-j** bearing an aryl instead of the alkyl substituent, we know that in the course of the reaction between the diazo compound **81** and chiral alcohols in the presence of $In(OTf)_3$, no racemization takes place.

(43) (a) Ohtani, I.; Kusumi, T.; Kashman, Y.; Kakisawa, H. *J. Am. Chem. Soc.* **1991**, *113*, 4092–4096. (b) Dale, J. A.; Mosher, H. S. *J. Am. Chem. Soc.* **1973**, *95*, 512–519.

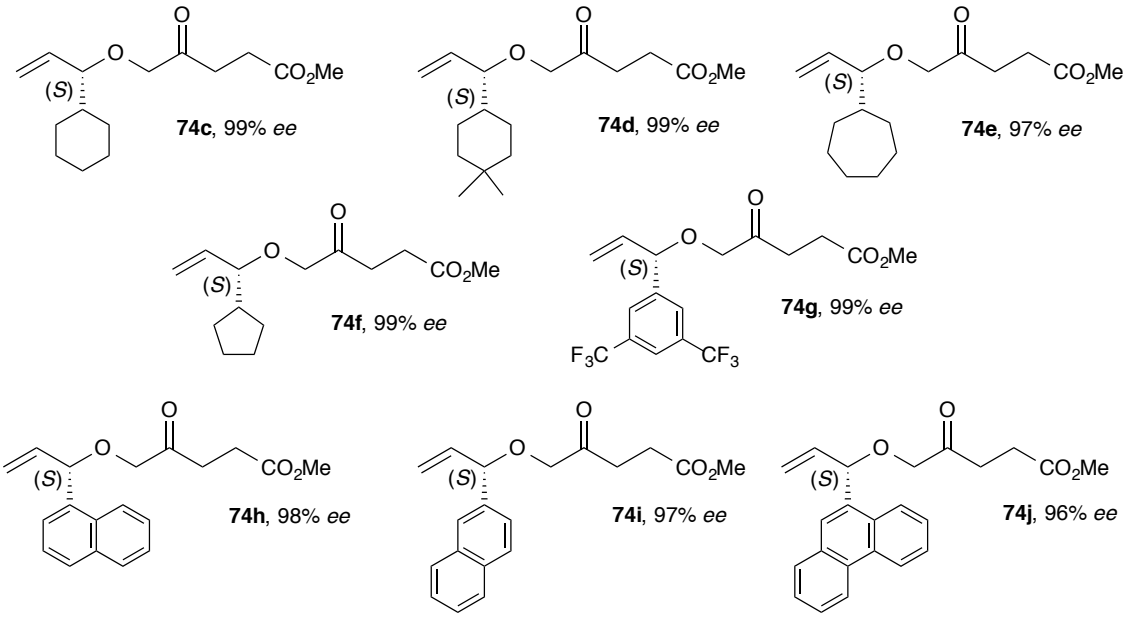
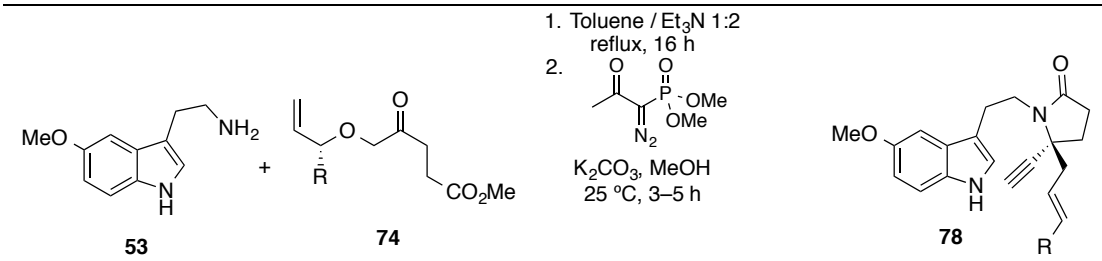


Figure 3. Chiral oxoesters **74c-j**.

All chiral oxoesters were subjected to previously developed optimized conditions for the double condensation / Claisen rearrangement. The results are summarized in Table 9. BisCF_3-phenyl **74g** (Table 9, entry 5) and 1-naphthyl **74h** (Table 9, entry 6) derivatives provided low enantioselectivities (69 : 31 *er*). 2-Naphthyl **74i** (Table 9, entry 7) and phenanthryl **74j** (Table 9, entry 9) substituents proved to be as efficient as the phenyl-based auxiliary (Table 9, entry 8; 80 : 20 *er*). When *c*-hexyl **74c** (Table 9, entry 2), *c*-heptyl **74e** (Table 9, entry 3) and 4,4-$(CH_3)_2$-*c*-hexyl **74d** (Table 9, entry 1) substituted oxoesters were used, the corresponding lactams were obtained with 85 : 15 *er*. We found that the best level of chirality transfer was achieved with R = *c*-pentyl (Table 9, entry 4; 89 : 11 *er*), affording enantioenriched alkyne **78f**, formed after [3,3]-sigmatropic Claisen rearrangement and homologation, in 71% yield over 2 steps.

Table 9. Investigation of the chiral auxiliary efficiency.



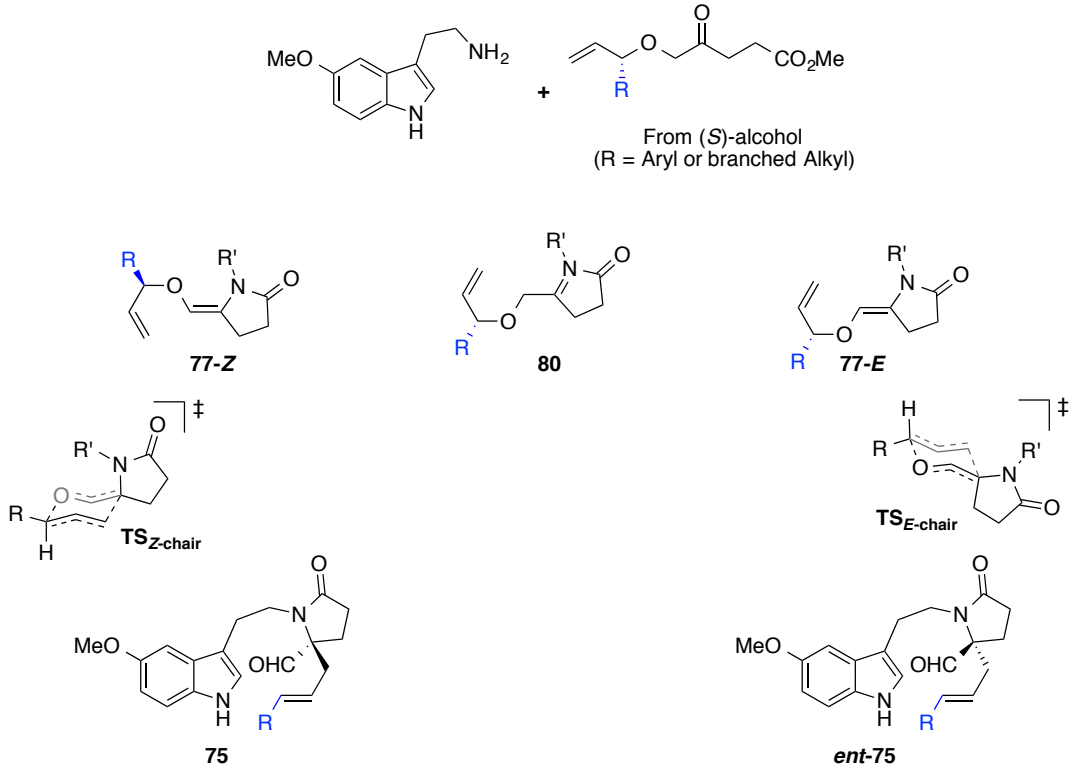
Entry	R	Oxoester	Yield of 78, %[a]	*er*[b]
1	4,4-$(CH_3)_2$-*c*-Hexyl	**74d**	71	85 : 15
2	*c*-Hexyl	**74c**	74	85 : 15
3	*c*-Heptyl	**74e**	66	86 : 14
5	c-Pentyl	**74f**	71	89 : 11
4	3,5-$(CF_3)_2C_6H_3$	**74g**	64	69 : 31
6	1-Naphthyl	**74h**	61	68 : 32
7	2-Naphthyl	**74i**	68	80 : 20
8	Phenyl[c]	**74b**	64	20 : 80
9	9-Phenanthryl	**74j**	70	80 : 20

Note: all reactions performed on a 0.05 mmol scale in a sealed MW vial. [a] Yield over 2 steps. [b] *er* measured on alkynes **78b-j** using chiral HPLC, IA column. [c] (*R*)-configured chiral oxoester used.

The development of an efficient method for the synthesis of the enantioenriched alkyne precursor for the key gold-catalyzed hydroarylation set the stage for the asymmetric synthesis of lundurines A–C, which will be discussed in the following section. In order to further understand the mechanism at play in the double condensation / Claisen rearrangement, several control experiments were carried out on ene-lactam intermediates **77-*E*** and **77-*Z*** presumably formed in this transformation.

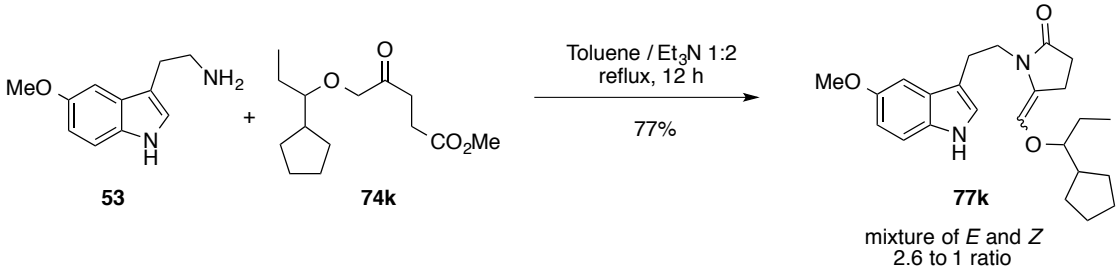
Mechanistic studies on ene-lactam intermediates 77-E and 77-Z

Initially, we had anticipated that during the tandem condensation / lactamization / [3,3]-sigmatropic Claisen rearrangement the system would be under Curtin-Hammett conditions, as a result of a fast equilibrium between pyrrolidinones **77-*Z*** and **77-*E*** by protonation of the exocyclic enol ether followed by deprotonation (Scheme 26).



Scheme 26. Proposed equilibrium between pyrrolidinones **77-*Z*** and **77-*E***.

To confirm this hypothesis we synthesized a closely related model oxoester **74k** lacking the olefin in the "allyl fragment". Subjecting the saturated model system to our optimized reaction conditions resulted in the formation of a mixture of *E*- and *Z*- pyrrolidinones **77** in a 2.6:1 ratio (Scheme 27).



Scheme 27. Synthesis of *E*- and *Z*-pyrrolidinones **77k**.

The two isomers could be partially separated and the pure fraction of each isomer was used in the equilibration experiments. To simulate the real reaction conditions, we added *ca.* 1 equiv of MeOH and 2 equiv of water. No equilibration was observed after heating at 100 °C in 1:2 toluene-Et_3N for several h (Figure 4).

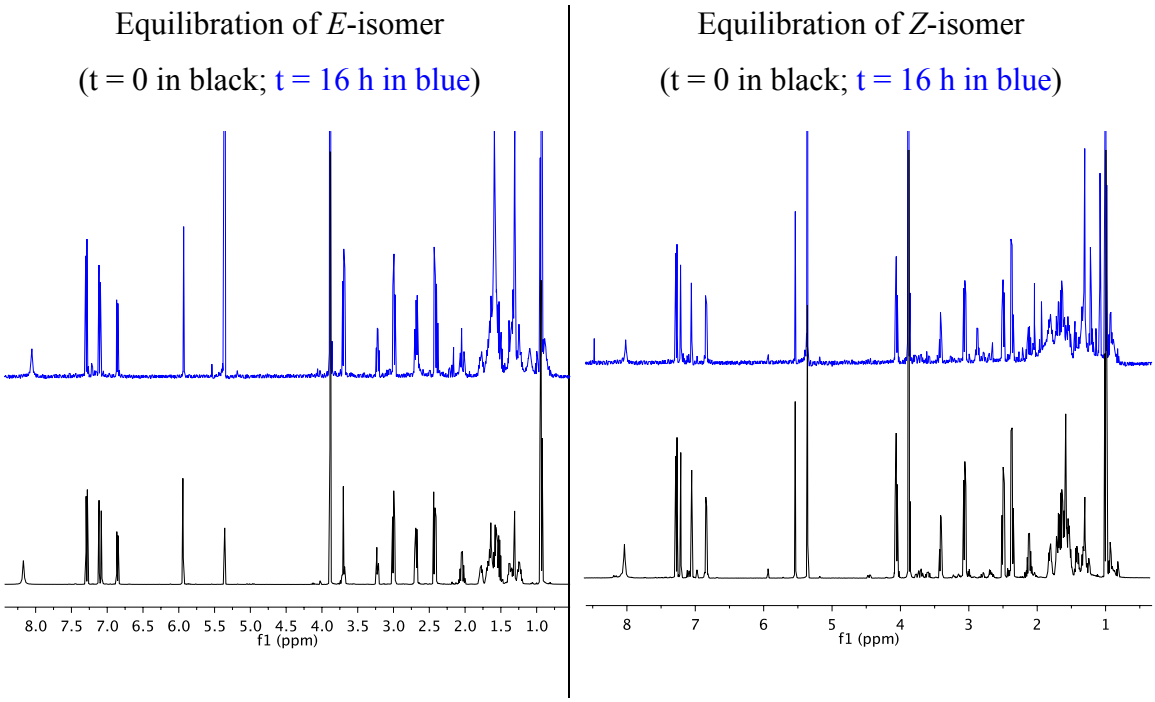
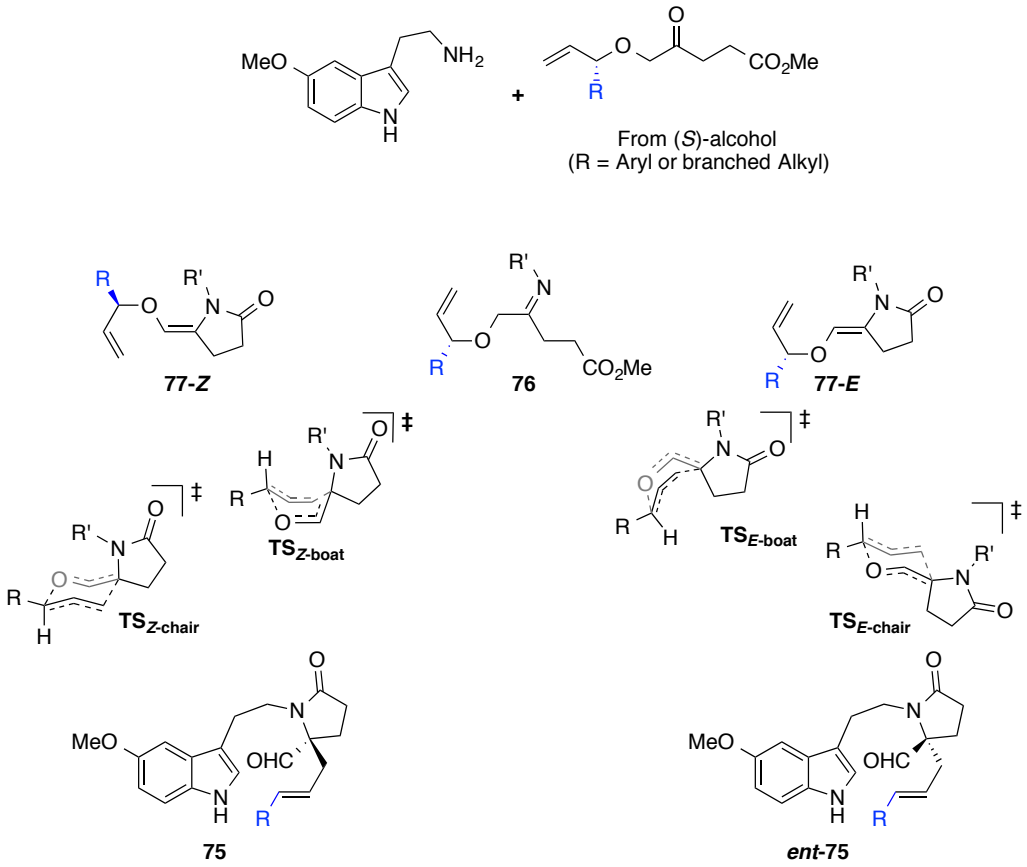


Figure 4. Equilibration studies of *E*- and *Z*-pyrrolidinones **75k**.

Based on these results we propose that the major **77-*E*** pyrrolidinone reacts preferentially through a boat-like transition state $\mathbf{TS}_{\boldsymbol{E}\textbf{-boat}}$ to form (*S*)-**75**, whereas the minor isomer **77-*Z*** reacts mainly through $\mathbf{TS}_{\boldsymbol{Z}\textbf{-chair}}$ (Scheme 28),[44] assuming that the Claisen rearrangement takes place after lactamization.

(44) Khaledy, M. M.; Kalani, M. Y. S.; Khuong, K. S.; Houk, K. N. *J. Org. Chem.* **2003**, *68*, 572–577.

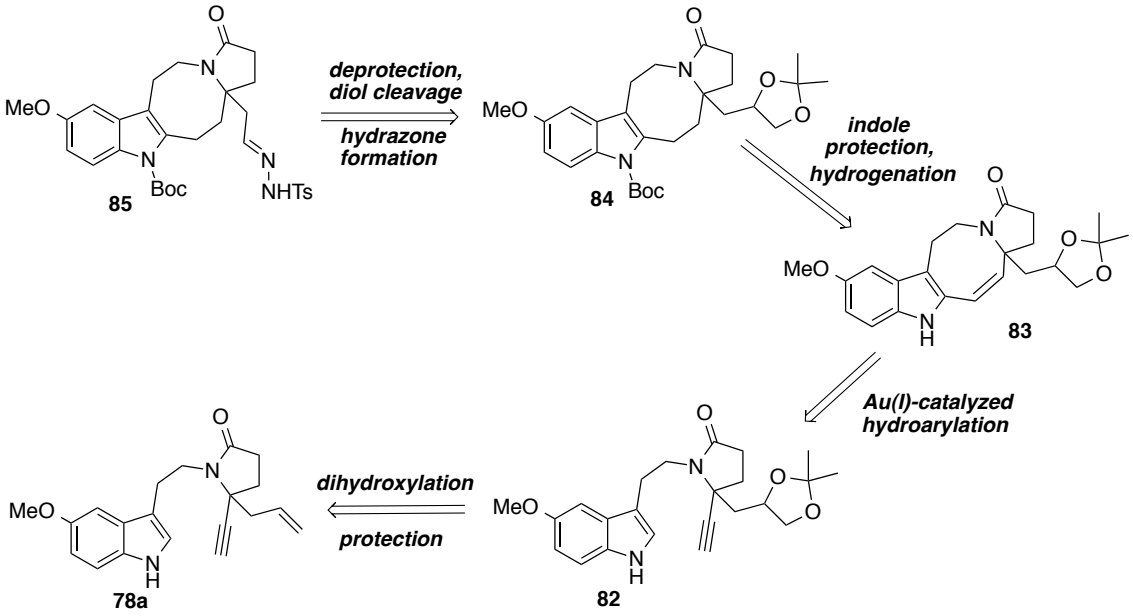


Scheme 28. Proposed mechanism for enantioselective Claisen rearrangement.

Although a condensation / [3,3]-sigmatropic Claisen rearrangement / lactamization sequence using the optimized conditions could also be proposed, we never observed the formation of cross-amide products or secondary amines after the condensation / Claisen rearrangement for any of the systems we examined.

Initial cyclopropanation strategy

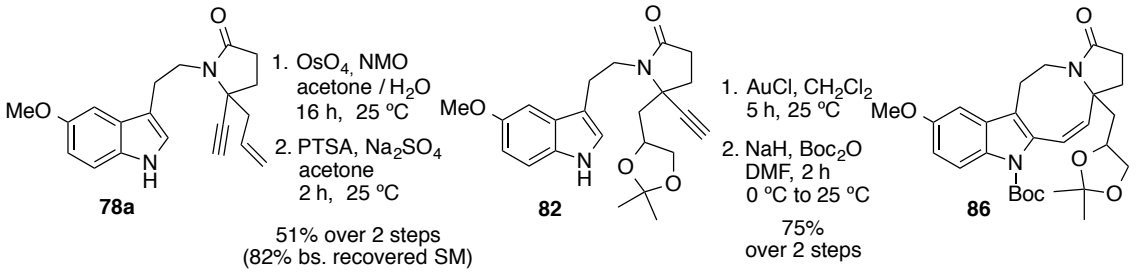
Since we developed an efficient method for the synthesis of the enantioenriched precursor **78f** for the key gold-catalyzed hydroarylation, we focused our attention on the next challenging transformation: the intramolecular cyclopropanation of indole, which would set the stage for the synthesis of lundurines A–C. Initially, we proposed the following retrosynthetic approach for the synthesis of carbene precursor **85** (Scheme 29).



Scheme 29. Retrosynthetic approach for the synthesis of hydrazone **85**.

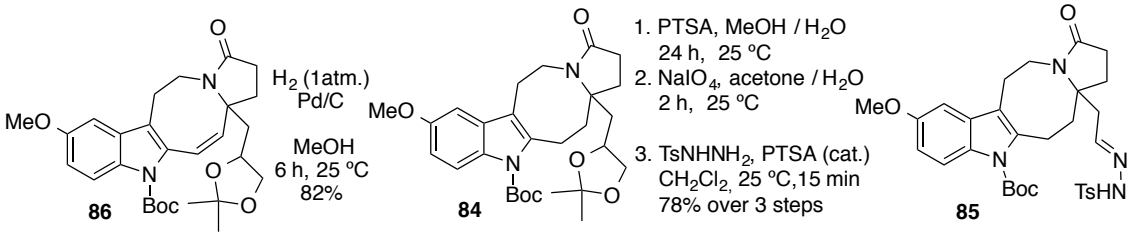
The desired carbene precursor **85** could be obtained from the indoloazocine precursor **84** *via* a deprotection / diol cleavage / hydrazine formation sequence. Protection of the indole nitrogen of **83** followed by hydrogenation would deliver acetonide **84**. For the model studies, we selected Boc as the protecting group instead of the labile methyl carbamate, present in the natural product. The main tetracyclic core of the molecule can be constructed by a gold(I)-catalyzed intramolecular hydroarylation of alkyne **78a**, which is easily accessible *via* the methods described previously.

The required alkyne **82** was synthesized from allyl lactam **78a** *via* dihydroxylation followed by protection of the diol as an acetonide (Scheme 30). The hydroarylation was accomplished with 5 mol% of gold(I) chloride providing tetracycle **83** with exquisite *endo*-selectivity. The indole nitrogen was protected as its *tert*-butyl carbamate under standard conditions, delivering the substrate **86** for a subsequent hydrogenation.



Scheme 30. Synthesis of pentacycle **86**.

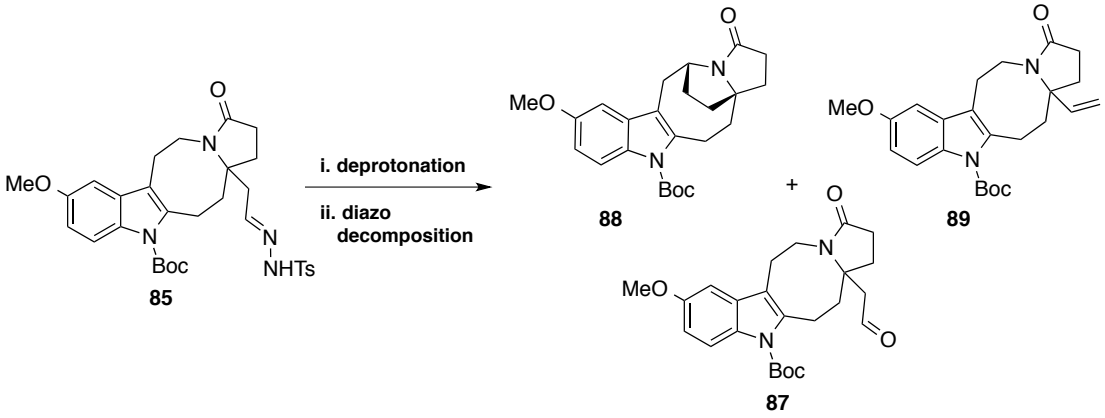
The catalytic hydrogenation of **86** with 2 mol % Pd/C afforded tetracycle **84** (Scheme 31) as well as its undesired overreduced indoline. The selectivity of this transformation proved to be difficult to control and hexahydroazocine **84** was obtained in *ca.* 80% yield. The synthesis of the corresponding aldehyde **87** was accomplished via a deprotection / oxidative cleavage sequence, that was performed "one-pot", by the removal of the volatiles before the addition of $NaIO_4$. Although this aldehyde could be isolated, it was converted into tosyl hydrazone without further purification, yielding **85** (78% from **84**).



Scheme 31. Synthesis of tosyl hydrazone **85**.

With carbene precursor **85** in hand, we started our investigation of a transition metal-catalyzed indole cyclopropanation. Although a systematic screening of bases, catalysts, and temperatures was carried out, only selected conditions are shown in Table 10. Despite our efforts, undesired vinyl-substituted tetracycle **89** was obtained as the major product in all cases. An unexpected formal C–H insertion was occurring in the presence of rhodium and copper salts. A control experiment was carried out in the absence of a metal catalyst, which led to the formation of vinyl derivative **89** the sole product (Entry 8).

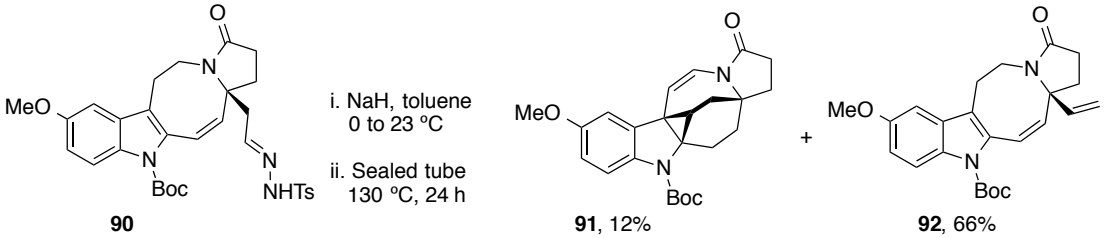
Table 10. Studies of cyclopropanation catalyzed by various transition metals.



Entry	Catalyst	Base	Temperature, °C	Outcome[a]
1	$Rh_2(OAc)_4$	K_2CO_3	75	**88** + **89**
2	$Rh_2(OAc)_4$	NaOMe	75	**88** + **89**
3	$Rh(EtCO_2)_2$	NaH	95	**88** + **89**
4	$Rh_2(OAc)_4$	NaH	95	**88** + **89**
5	Rh_2(*s*-DOSP)$_4$	NaH	95	**88** + **89**
6	$Rh_2(OAc)_4$	NaH	130	**88** + **89**
7	$Rh_2(OAc)_4$	NaH	130	**88** + **89**
8	–	NaH	130	**89**
9	CuIPrCl	NaH	75	**87** + **88** + **89**
10	CuIPrCl + NaBArF	NaH	75	**87** + **88** + **89**
11	$Cu(OTf)_2$	NaH	95	**87** + **88** + **89**
12	[Tp^{Br3}Cu(NCMe)]	NaH	95	**87** + **88** + **89** +**85**

Note: all reactions performed on a 0.02 mmol scale with 100 mol% of base, 10 mol% of catalyst, in a 0.1 M solution in toluene, in a sealed MW vial. [a] Determined by GC.

However, when transition metal-free conditions were used for the system featuring a partially unsaturated hexahydroazocine ring system **90**, cyclopropane **91** was obtained albeit in low yield (Scheme 32). As will be discussed later, a remarkable double bond migration had also occurred in this transformation.



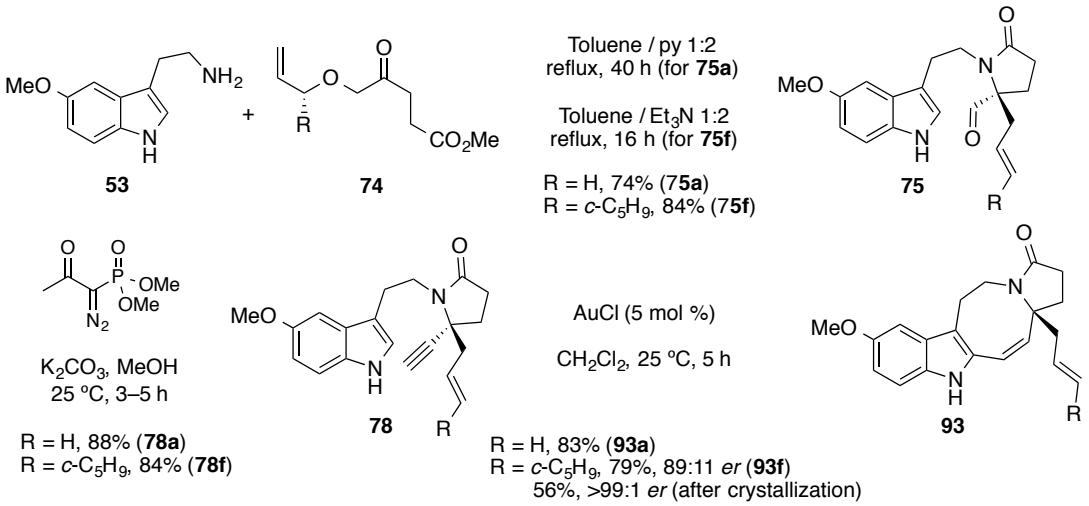
90 **91**, 12% **92**, 66%

Scheme 32. Formation of vinylcyclopropane **91**.

We were pleased to observe the direct cyclopropanation and formation of **91** through deprotonation of the hydrazone **90** and generation of the corresponding diazo compound. This finding provided an entry into the synthesis of lundurines A–C.

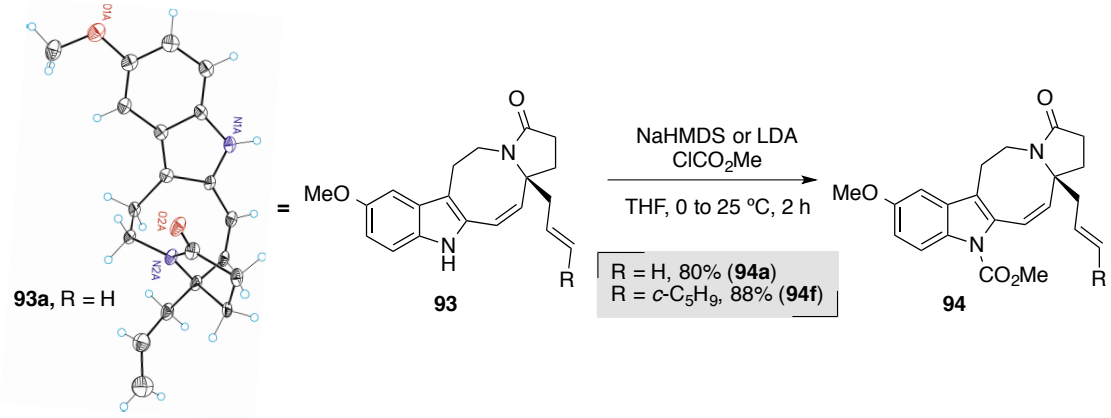
Syntheses of racemic and enantiopure lundurines A – C

Applying the optimal conditions found for the condensation of oxoester **74** with commercially available 5-methoxytryptamine, we obtained high yields of lactams (R = H: **75a** 74%; R = *c*-pentyl, **75f** 84%), formed after [3,3]-sigmatropic Claisen rearrangement (Scheme 33). Aldehyde 7**5** was immediately homologated into the corresponding alkyne **78** employing Ohira-Bestmann reagent (**78a** 88%; **78f** 84%, 89:11 *er*), setting the stage for the proposed key 8-*endo*-*dig* gold(I)-catalyzed hydroarylation.



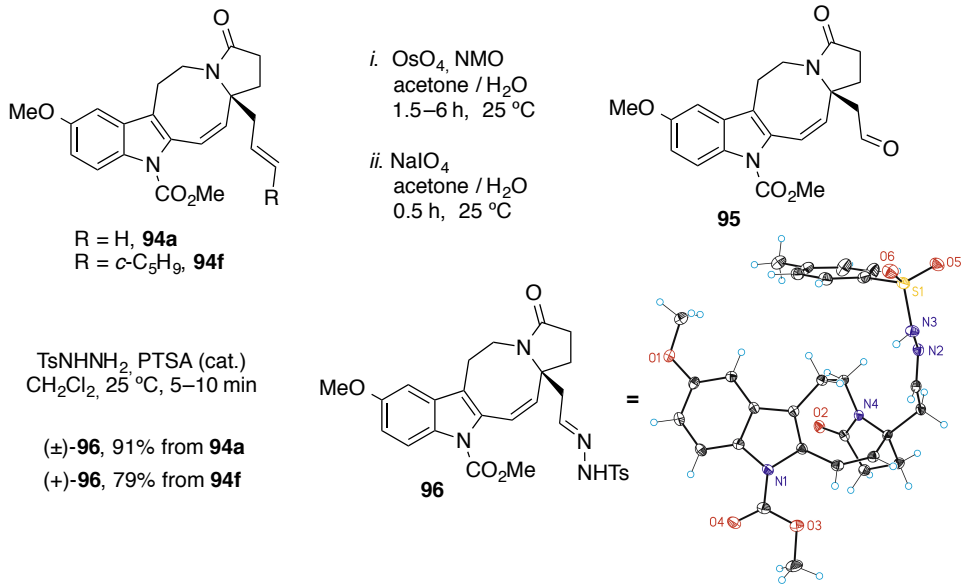
Scheme 33. Synthesis of tetracycles **93a** and **93f**.

Based on preliminary studies, we knew that AuCl provides perfect 8-*endo* selectivity and high yields of the desired tetracycle **93**. The products of gold(I)-catalyzed hydroarylation were obtained with 5 mol% catalyst loading (**93a** 83%; **93f** 79%, 89:11 *er*). Tetracycles **93** are highly crystalline and **93f** was crystallized to obtain virtually enantiopure material (mother liquor, 56%, >99:1 *er*) and the structure of **93a** was confirmed by single crystal X-ray diffraction. When [IPrAu(NCMe)]SbF_6 (5 mol%) was used as a catalyst, we isolated indoloazocine **93a** in 95% yield (0.62 mmol scale), however we elected to use gold(I) chloride during scale up for economical reasons. The required methyl carbamate at the indole nitrogen was then introduced using NaHMDS or LDA as the base (**94a** 80%; **94f** 88%) (Scheme 34).



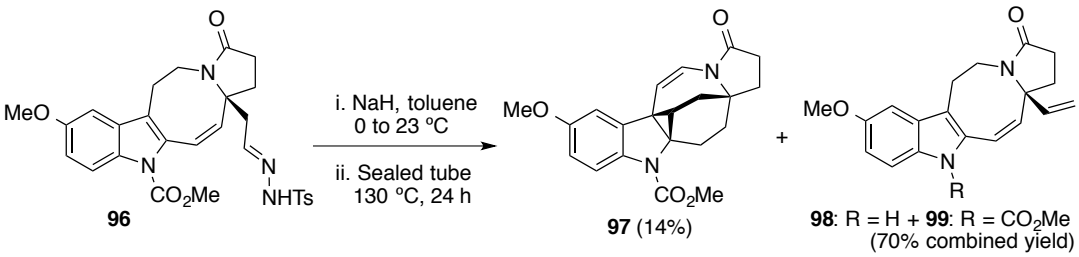
Scheme 34. Synthesis of methyl carbamate protected indole **94**. ORTEP representation of the X-ray crystal structure of **93a**. 50% probability of the thermal ellipsoids.

The exocyclic olefin of **94** was converted to the corresponding aldehyde **95** *via* a dihydroxylation / oxidative cleavage sequence (**94** → **95**), that was performed "one-pot", by the removal of the volatiles before addition of $NaIO_4$. Although this aldehyde **95** could be isolated, it was routinely converted without further purification into tosyl hydrazone **96** ((±)-**96**, 91% and (+)-**96**, 79% from **94**, Scheme 35). The absolute configuration of (+)-**96** was determined by single crystal X-ray diffraction, confirming the C20 (*S*)-configuration of all previous intermediates.



Scheme 35. Synthesis of enantiopure hydrazone (+)-**96**. ORTEP representation of the X-ray crystal structure of (+)-**96** (the solvent -acetonitrile- was omitted for clarity) 50% probability of the thermal ellipsoids. (*S*) absolute configuration at the C20 stereocenter.

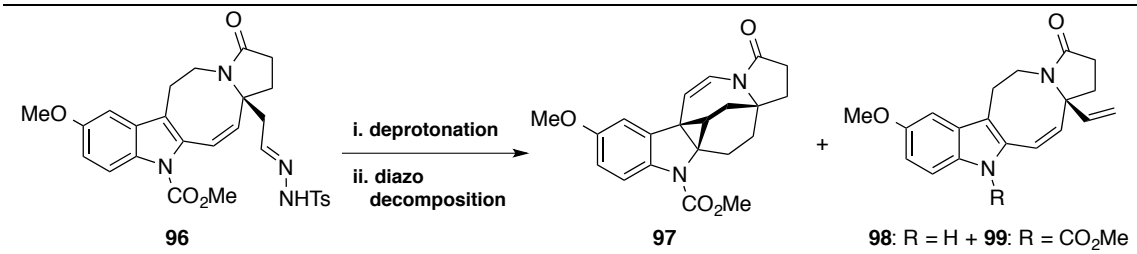
As discussed in the previous section, initial attempts to perform the cyclopropanation by various transition metal-catalyzed procedures were unsuccessful. The direct cyclopropanation and formation of **97** through deprotonation of the hydrazine **96** generation of the corresponding diazo compound was possible, although only low yields of the desired cyclopropane **97** were obtained. Most surprising was the fact that in **97** the double bond had migrated to the opposite side of the hexahydroazocine ring (Scheme 36).



Scheme 36. Direct cyclopropanation of indole.

Although a systematic screening of bases, solvents, concentrations and temperatures was performed, only selected conditions are showed in Table 11. Unfortunately, none of the conditions tested favored the formation of vinylcyclopropane **97** as the main product.

Table 11. Studies of the direct cyclopropanation.

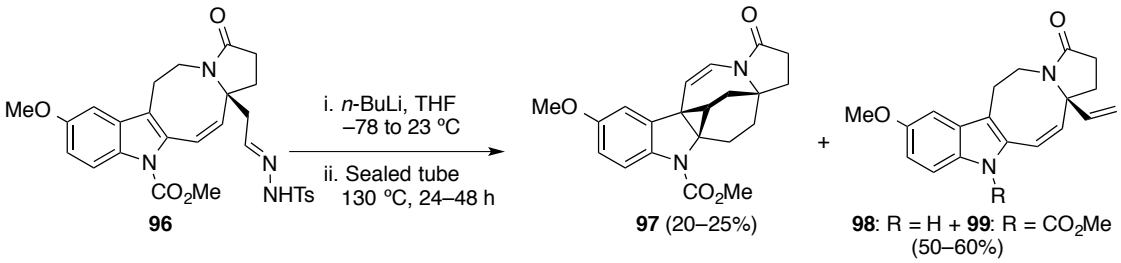


96 **97** **98**: R = H + **99**: R = CO_2Me

Entry	Base	Additive	Solvent	Temterature, °C[a]	97/(98 + 99) ratio[b]
1	NaH	−	toluene	0 / 130	1 : 4.9
2	NaH	−	toluene	0 / 60	–[d]
3	NaH	−	dioxane	0 / 120	1 : 4.3
4	NaHMDS	−	$(MeOC_2H_4)_2O$	0 / 130	1 : 2.8
5	NaHMDS	−	toluene	0 / 130	1 : 3.1
6	NaHMDS	−	THF	0 / 130	1 : 4.1
7	NaHMDS	−	DMSO	0 / 130	traces / 10
8	NaHMDS	−	toluene/THF	0 / 130	1 : 3.1
9	NaHMDS	−	THF	0 / 145	1 : 7
10	NaHMDS	TsNa	DMSO	0 / 130	–[e]
11	KHMDS	−	THF	0 / 130	1 : 2.5
12	KHMDS	18-crown-6	THF	0 / 130	1 : 3.0
13	*n*-BuLi	−	THF	-78 / 130	1 : 2.0
14	*n*-BuLi	LiCl	THF	-78 / 130	–[e]
15	*t*-BuP_4	−	THF	0 / 130	–[f]
16[g]	NaH	$Cu(TBS)_2$	toluene	0 / 90	traces / 10

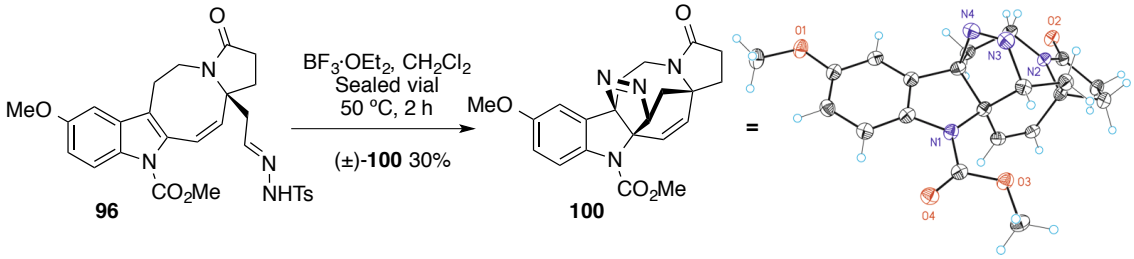
Note: all reactions performed on a 0.05 mmol scale with 1 equivalent of base, in a 0.025 M solution in a sealed MW vial. [a] Temperature of the base addition / decomposition of the hydrazone salt. [b] Determined by GC. [d] No decomposition of hydrazone salt. [e] Only mixture of protected and unprotected vinyl-substituted tetracycles, product of cyclopropanation was not detected. [f] Decomposition of starting material. [g] Conditions developed by Qin and co-workers.[17]

In spite of our efforts, we were unable to obtain yields higher than 20–25% in this transformation and the main products of the reaction were the undesired vinyl-substituted tetracycles **98** and **99** (Scheme 37).



Scheme 37. Optimized reaction conditions for the direct indole cyclopropanation.

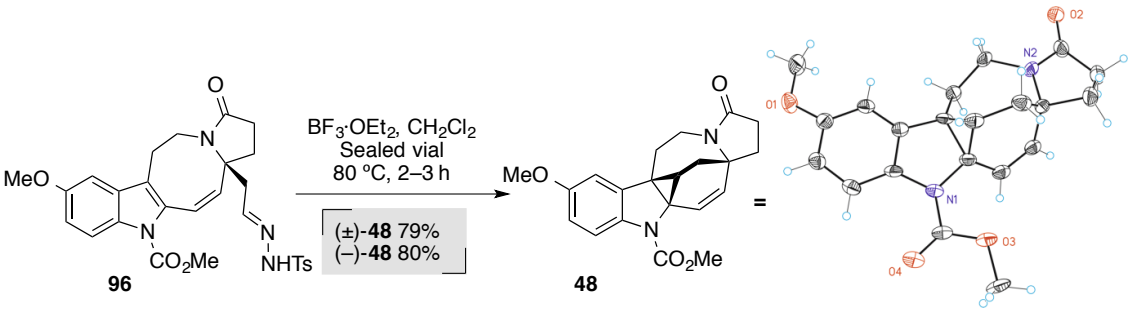
In the course of our investigations, we isolated pyrazoline **100**, whose structure was confirmed by NMR spectroscopy and X-ray diffraction (Scheme 38). This is the first example of a stable formal [3+2] dipolar cycloadduct between a diazocompound and an indole. Interestingly, pyrazolines originating from formal [3+2] cycloadditions of di- and tri-substituted olefins with tosyl hydrazones in the presence of Lewis acids have been reported.[45,46,47]



Scheme 38. Synthesis of pyrazoline **100**. ORTEP representation of the X-ray crystal structure of **100**. 50% probability of the thermal ellipsoids.

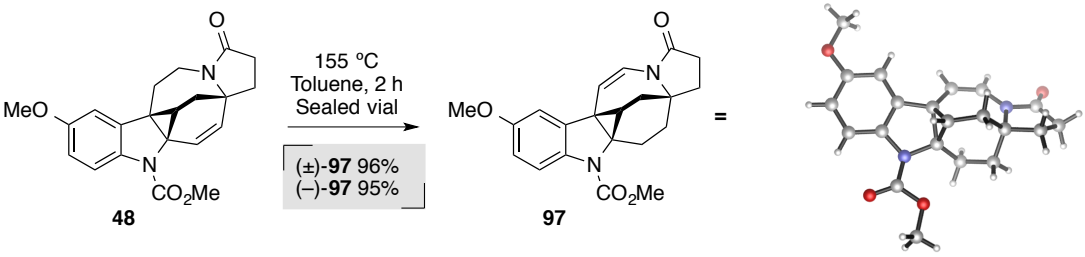
With the aim of using this intermediate to our advantage, we found that under acidic conditions related to the abovementioned studies, the desired cyclopropanation occurred in high yield. Thus, treatment of **96** with $BF_3{\cdot}OEt_2$ in CH_2Cl_2, at 80 °C in a sealed vial gave **48** in 79–80% yield (Scheme 39), whose structure was confirmed by X-ray diffraction.

(45) Frank, É.; Mucsi, Z.; Zupkó, I.; Réthy, B.; Falkay, G.; Schneider, G.; Wölfling, J. *J. Am. Chem. Soc* **2009**, *131*, 3894–3904.
(46) Padwa, A.; Ku, H. *J. Org. Chem.* **1980**, *45*, 3756–3766.
(47) Schultz, A. G.; Eng, K. K. *Tetrahedron Lett.* **1986**, *27*, 2331–2334.



Scheme 39. Synthesis of vinyl cyclopropane **48**. ORTEP representation of the X-ray crystal structure of **48**. 50% probability of the thermal ellipsoids.

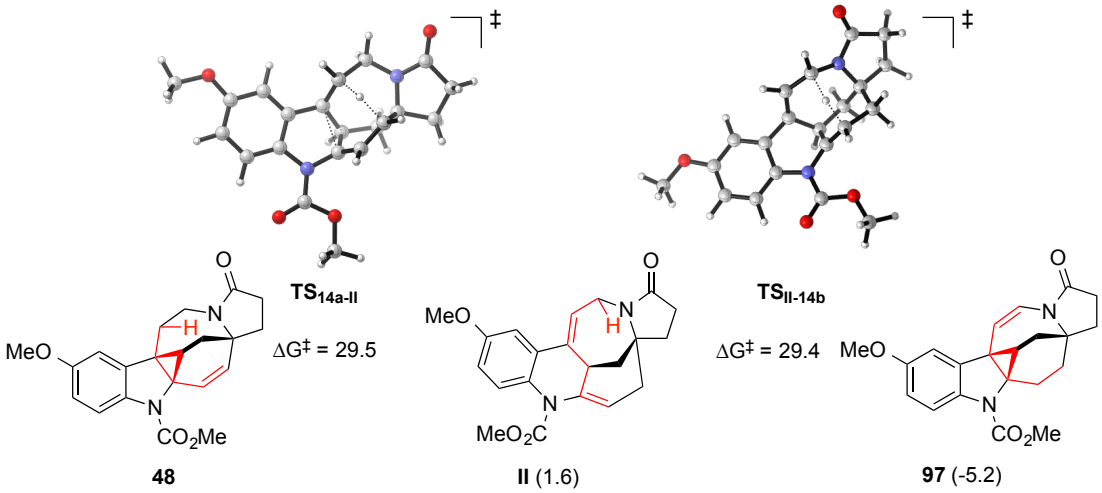
Remarkably, this product of direct cyclopropanation (**48**) could be converted in essentially quantitative yield into its isomer **97** by simple heating at 155 °C for 2 h (Scheme 40).



Scheme 40. The olefin isomerization. CYLview depiction of the X-ray crystal structure of (–)-**97**, (*S*) absolute configuration at the C20 stereocenter.[48,49,50]

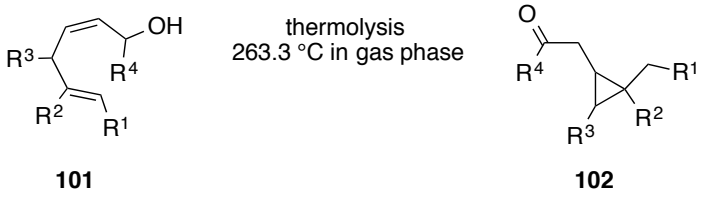
This puzzling isomerization of **48** into **97** most likely proceeds by a homodienyl retro-ene rearrangement[51] followed by the reverse process, in which the resulting 1,4-diene **II** leads to a new vinyl cyclopropane moiety in **97**, *via* an intramolecular ene reaction (Scheme 41).

(48) In order to determine the absolute structure high resolution data was collected using Molybdenum radiation and applying methodology described in: Escudero-Adán, E. C.; Benet-Buchholz, J. B.; Ballester, P. *Acta Cryst.* **2014**, *B70*, 660–668. The absolute configuration could be determined reliably with a Flack value based on Parsons' quotients of 0.00(8).
(49) Flack, H. D. *Acta Cryst.* **1983**, *A39*, 876–881.
(50) Parsons, S.; Flack, H. *Acta Cryst.* **2004**, *A39*, S61.
(51) Hudlicky, T.; Koszyk, F. J. *Tetrahedron Lett.* **1980**, *21*, 2487–2490.



Scheme 41. Mechanism for the migration of the olefin from **48** to **97** *via* homodienyl retro-ene / ene rearrangement. Numbers in parenthesis correspond to relative free energies in kcal·mol^{-1} (B3LYP/6-31G(d), solvent = toluene).

This type of transformation has been studied before in cyclic and bicyclic systems, leading irreversibly to skipped dienes.[52] The homodienyl retro-ene rearrangement of bicyclo[5.1.0]octen-2-ene has been reported to take place at 150-170 °C to furnish 1,4-cyclooctadiene with an activation energy of *ca*. 33 kcal·mol^{-1}. The reverse process, the formation of vinyl cyclopropanes from skipped dienes under thermal conditions, has only one precedent in the oxy-homodienyl rearrangement (Scheme 42), which requires temperatures of around 260 °C (activation energies of 41-43.5 kcal·mol^{-1}).[53]



	R1	R2	R3	R4	Yield, %
a	H	H	H	H	82
b	H	H	CH_3	H	90
c	CH_3	H	CH_3	H	85
d	H	CH_3	H	H	75
e	H	H	H	CH_3	85

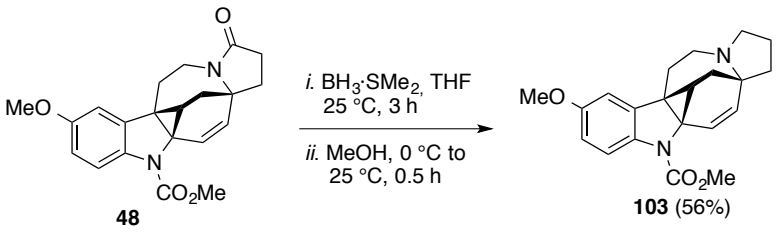
Scheme 42. The reported oxy-homodienyl rearrangement.[53]

According to DFT calculations (Scheme 41), the two transition states for the hydrogen shifts in our system have similar energies (*ca*. 29.5 kcal·mol^{-1}) and the formation of a

(52) (a) von E. Doering, W.; Roth, W. R. *Angew. Chem. Int. Ed.* **1963**, *2*, 115–122. (b) Ellis, R. J.; Frey, H. M. *Proc. Chem. Soc.* **1964**, 221. (c) Grimme, W. *Chem Ber.* **1965**, 756–763. (d) Glass, D. S.; Boikess, R. S.; Winstein, S. *Tetrahedron Lett.* **1966**, *7*, 999–1008. (e) Parziale, P. A.; Berson, J. A. *J. Am. Chem. Soc.* **1990**, *112*, 1650–1652. (g) Parziale, P. A.; Berson, J. A. *J. Am. Chem. Soc.* **1990**, *113*, 4595–4606. (e) Hudlicky, T.; Kutchan, T. N.; Naqvi, S. M. *Org. React.* **1985**, *33*, 247–335.
(53) Klärner, F.-G.; Rüngeler, W.; Maifeld, W. *Angew. Chem.* **1981**, *93*, 613–614.

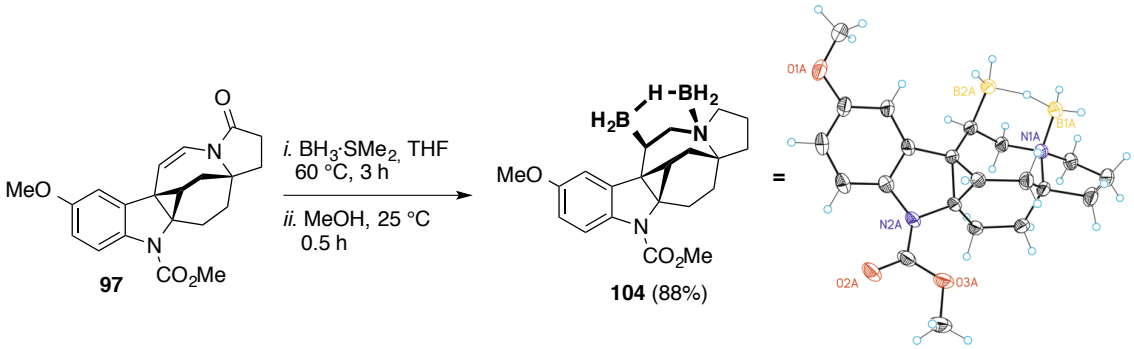
more stable conjugated *N*-acylenamine drives the equilibrium towards the formation of **97**. An alternative direct dyotropic rearrangement of **48** into **97** is highly unlikely, since the computed barrier of activation for this process would be very high (>80 kcal·mol^{-1}).

Isomers **48** and **97** behave very differently in their reactions with borane. When **48** was treated with a large excess of BH_3·SMe_2, the olefin remained intact and exclusive reduction of the lactam was observed to form tertiary amine **103** in moderate yield (56%) (Scheme 43).



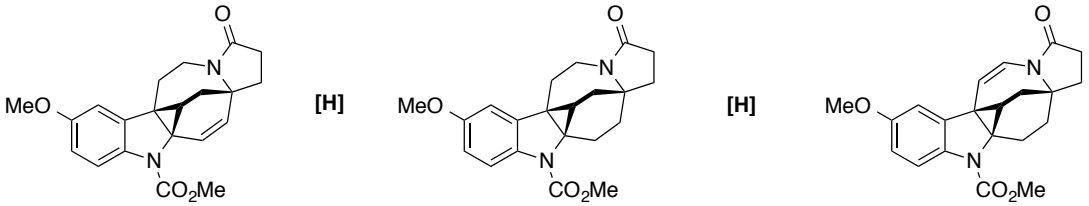
Scheme 43. Reduction of **48** with borane**.**

Subjecting **97** to the similar conditions led to the formation of unexpected hydride-bridged diborylated heptacycle **104**, which showed remarkable stability towards hydrolysis. The structure of **104** was unambiguously assigned by X-ray diffraction (Scheme 44).



Scheme 44. Reduction of **97** with borane. ORTEP representation of the X-ray crystal structure of (±)-**104** (one rotamer omitted for clarity). 50% probability of the thermal ellipsoids.

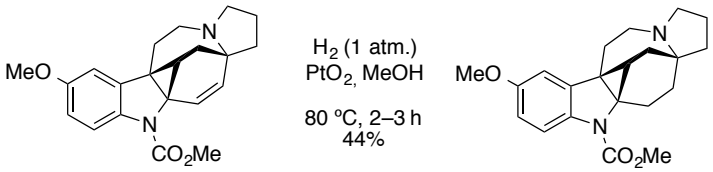
Since a direct double reduction with borane failed for both isomers **48** and **97**, we resorted to perform the transition metal-catalyzed hydrogenation of the olefin of **48** or **97** prior to reduction of the lactam (Scheme 45).



Scheme 45. Designed hydrogenation of **48** and **97**.

For our investigation, we selected Pd/C, Raney nickel, Wilkinson, Adams and Crabtree's catalysts as transition metal sources. Unfortunately, vinylcyclopropane **48** was recovered intact in all cases. Isomer **97** showed no reactivity with Adams catalyst, but underwent a cyclopropane opening when other catalysts were employed. Reduction of **97** with diimide also proved to be inefficient.

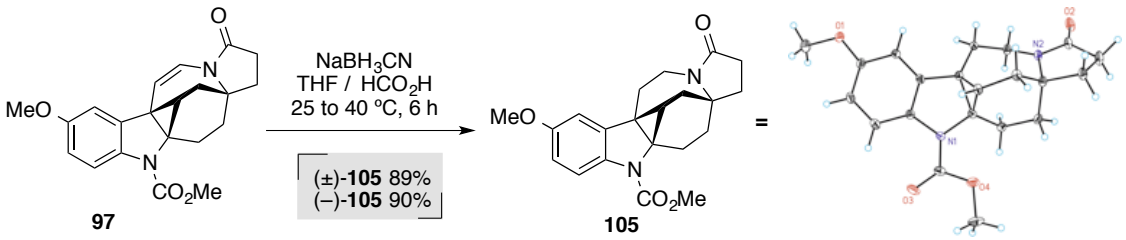
The hydrogenation of the olefin of **48** prior to borane reduction of the lactam failed, hydrogenation of **103** using PtO_2 as the precatalyst gave lundurine C (**3**), although in low yield (Scheme 46).



Scheme 46. Hydrogenation of **103** using PtO_2.

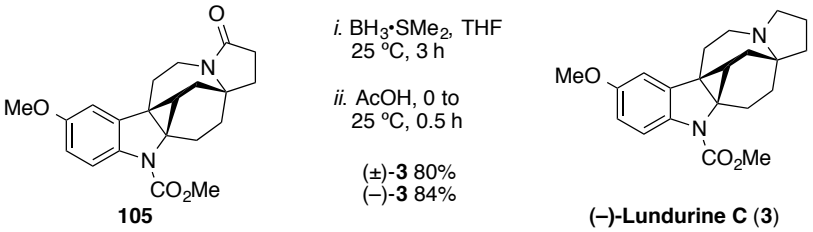
Gratifyingly, the reduction of the *N*-acylenamine double bond with $NaBH_3CN$[54] in the presence of formic acid afforded the saturated lactam **105** ((±)-**105**, 89% and (−)-**105**, 90%) (Scheme 47). The ready access to **105** led to a considerably more efficient synthesis of **3** and, more importantly, provided an entry to the synthesis of lundurines A (**1**) and B (**2**).

(54) Yazici, A.; Pyne, S. G. *Org. Lett.* **2013**, *15*, 5878–5881.



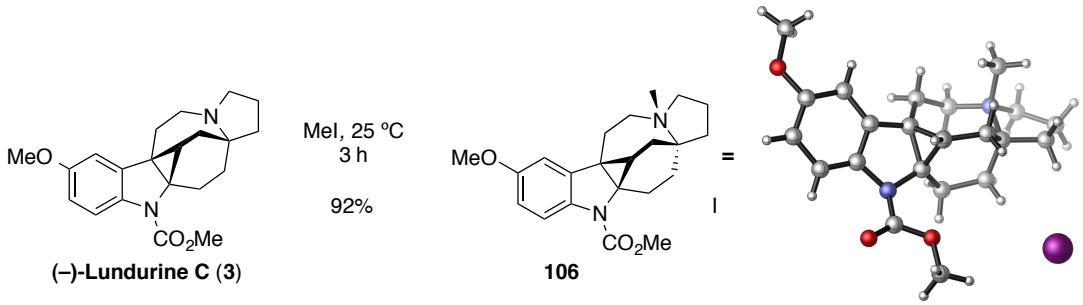
Scheme 47. Reduction of **97** with $NaBH_3CN$. ORTEP representation of the X-ray crystal structure of **105.** 50% probability of the thermal ellipsoids.

Hence, the first total synthesis of lundurine C (**3**) could be completed in one step from **105** by a second reduction with $BH_3{\cdot}SMe_2$ (Scheme 48). Surprisingly, enantiopure lundurine C (**3**) presented an optical rotation ([α_D^{589} = –1.1 ± 0.6°, $CHCl_3$, *c* 0.98, 300K] and [α_D^{589} = –6.2 ± 0.8°, CH_2Cl_2, *c* 0.3, 301K]) differing significantly from the one reported for the natural product [α_D^{589} = – 25°, $CHCl_3$, *c* 0.067],[9,10] although chiral HPLC analysis of our synthetic sample of lundurine C left no doubt with regards to its enantiopurity.



Scheme 48. Reduction of **105** with borane.

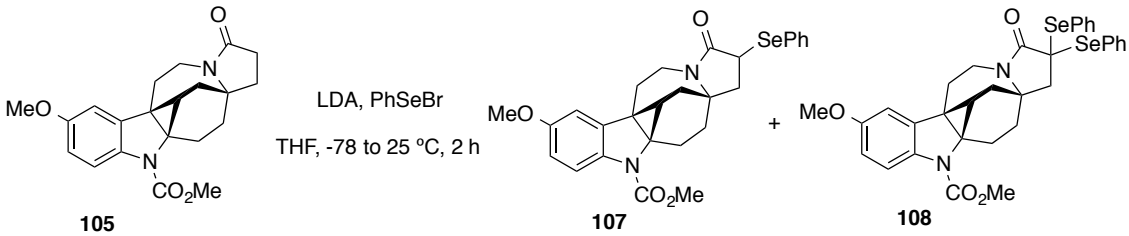
Furthermore, we prepared crystalline quaternary ammonium iodide **106**, whose absolute configuration was established by X-ray crystallography (Scheme 49). The discrepancy in the value of the optical rotation may have been caused by the very low concentration at which the natural product was measured originally that induced a significant error on the measurement.



Scheme 49. Quaternary ammonium iodide **106**. CYLview depictions of the X-ray crystal structures of enantiopure iodide salt **106** with absolute configuration.

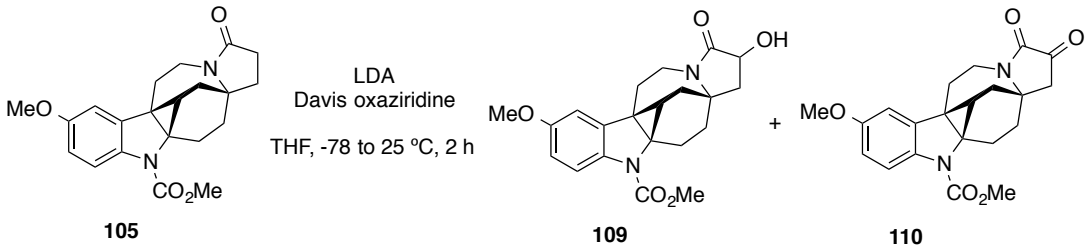
With the synthesis of lundurine C accomplished, we focused our efforts on developing an efficient procedure to obtain lundurines A and B. Having a common precursor **105** lacking the unsaturation in the lactam fragment in hand, we envisioned to introduce the olefin *via* α-selenylation of the amide followed by oxidation to selenoxide and concomitant elimination.

Unfortunately, low yields of the mono α-selenylation product **107** were observed with LDA and benzeneselenyl bromide and the product of diselenylation **108** was formed preferentially (Scheme 50). Variation of temperatures, bases, phenyl selenating reagents and order of addition did not lead to a satisfactory outcome.



Scheme 50. α-Selenylation of amide **105**.

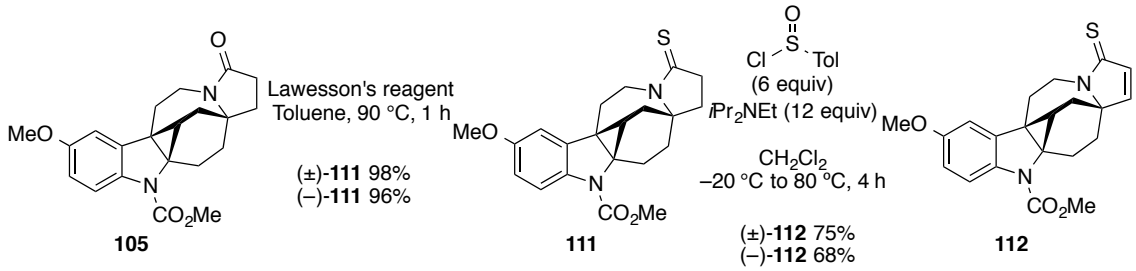
α-Hydroxylation of amide **105** with Davis oxaziridine proved to be ineffective (Scheme 51). Low yields of secondary alcohol were obtained because of its rapid *in situ* oxidation into the corresponding dicarbonyl compound **110**. Similar results were obtained in the case of molecular oxygen and $(TMSO)_2$ as oxidants. The Saegusa oxidation of corresponding silyl enol ether using a stoichiometric amount of Pd(II) acetate led to the extensive decomposition of the starting material.



Scheme 51. α-Hydroxylation of amide **105**.

In spite of our efforts, these approaches did not allow us to develop a reliable method to introduce an unsaturation in the lactam fragment. However, based on the work of Magnus,[55] we proposed a new strategy for the synthesis of lundurines *via* a thiolactam manifold.

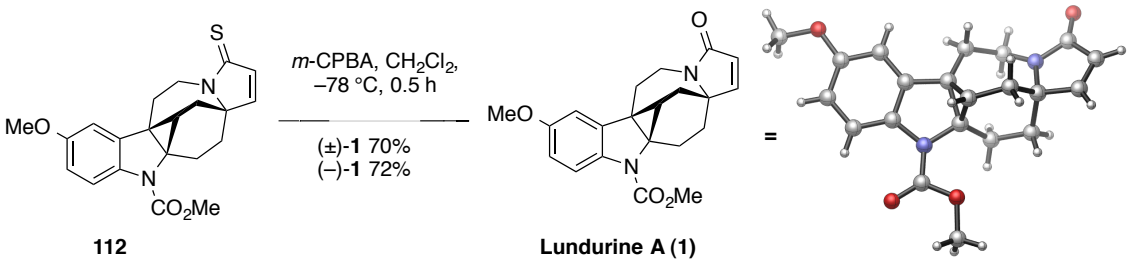
Lundurines A (**1**) and B (**2**) were both prepared in three additional steps from **105**, by thiolation / *C*-sulfinylation-elimination[55] (Scheme 52) and either oxidation or reduction. Intermediate **105** was first subjected to Lawesson's reagent to form thiolactam **111**, which then reacted with *para*-toluenesulfinyl chloride[56] in the presence of Hünig's base to generate *in situ* an α-sulfinyl thiolactam. Upon heating at 80 °C, a Cope-type elimination of the sulfinyl substituent was observed giving thiolundurine A (**112**).



Scheme 52. Synthesis of thiolundurine A (**112**).

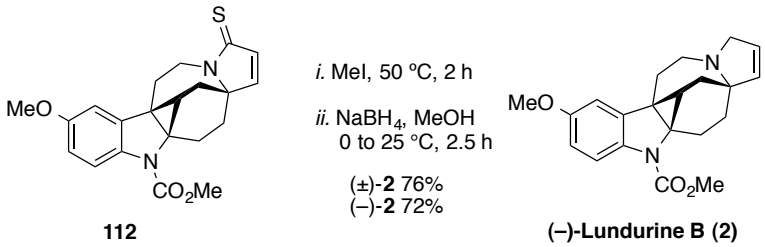
The oxidation of **112** with *m*-CPBA at –78 °C produced (–)-lundurine A (**1**) in 72% yield (Scheme 53). Interestingly, in contrary to that reported in the isolation and previous syntheses, racemic and enantiopure lundurine A are crystalline solids and we were able to obtain the first crystal structure of this natural product, which confirms its absolute configuration and the one of the whole family of natural compounds.

(55) Magnus, P.; Pappalardo, P. A. *J. Am. Chem. Soc.* **1986**, *108*, 212–217.
(56) Kurzer, F., *Org. Synth.* **1954**, *34*, 93.



Scheme 53. Formation of lundurine A (**1**). CYLview depictions of the X-ray crystal structures of enantiopure lundurine A (–)-**1**.

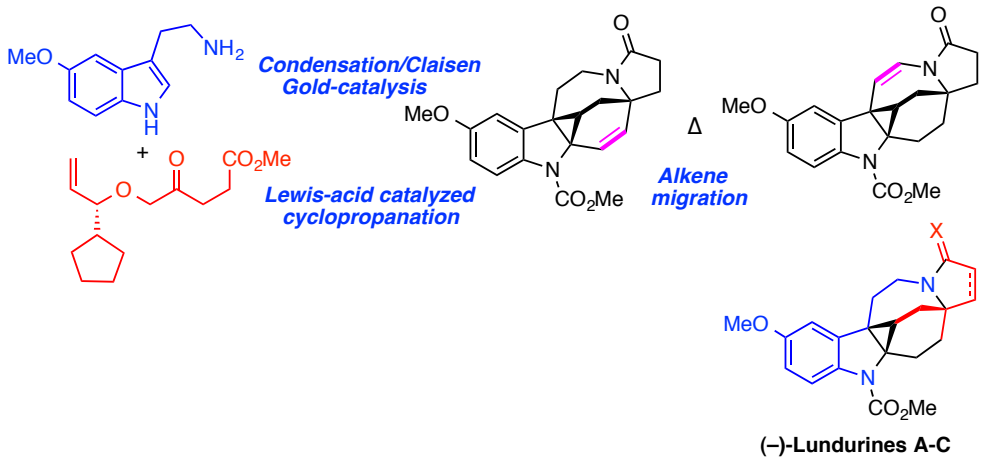
(–)-Lundurine B was obtained by simple reduction of the thiolactam, performed according to the procedure described by Magnus and co-workers.[55] The treatment of thiolactam **112** with iodomethane followed by sodium borohydride delivered **2** in 72% yield (Scheme 54).



Scheme 54. Synthesis of (–)-lundurine B.

Conclusions

A unified approach towards the synthesis of the natural products lundurines A–C has been developed, and successfully applied in the first total syntheses of racemic and enantiopure lundurine C as well as the total syntheses of racemic and enantiopure lundurines A and B (Scheme 55). The absolute configuration of lundurine C has been assigned as (5a*R*,5b*S*,6a*R*,12a*R*) by the X-ray crystal structure of its *N*-Me ammonium salt and the structure of lundurine A was confirmed by the first single crystal X-ray diffraction analysis of this natural product. Our synthesis of the lundurines is the shortest and most efficient to date (12–14 steps from known chiral alcohol **79f**, 6.6% overall yield for lundurine C and 3% overall yield for lundurines A and B, >99:1 *er*) and is perfectly suited for the preparation of a library of analogues for biological evaluation and also for its extension to the synthesis of other *Kopsia* alkaloids.



Scheme 54. Total synthesis of lundurines A – C.

After optimization of the chiral auxiliary, the generation of the C20 stereocenter was achieved by the implementation of a practical chirality transfer in a tandem condensation / lactamization / [3,3]-sigmatropic Claisen rearrangement, with a good level of enantioselectivity. We took advantage of a highly *8-endo-dig* selective hydroheteroarylation strategy using gold(I) as the catalyst in order to build the polyhydroazocine ring. Additionally, a new intramolecular cyclopropanation of indoles was developed by the formation of a pyrazoline, proceeding by formal [3+2] cycloaddition of a Lewis acid-coordinated hydrazone and a subsequent C–C bond formation through the loss of dinitrogen and toluenesulfinic acid. In the course of our investigations, a remarkably facile olefin migration through a vinyl cyclopropane retro-

ene / ene rearrangement was found and applied to the synthesis of this family of alkaloids. Finally, the challenging late stage functionalization was achieved by thiolation / *C*-sulfinylation-elimination and either oxidation or reduction strategy.

Experimental section

General Information

Unless otherwise stated, reactions were carried out under argon atmosphere in solvents dried by passing through an activated alumina column on a PureSolv^{TM} solvent purification system (Innovative Technologies, Inc., MA). Analytical thin layer chromatography was carried out using TLC-aluminium sheets with 0.2 mm of silica gel (Merck GF_{234}) using UV light as the visualizing agent and an acidic solution of vanillin or anisaldehyde in ethanol as the developing agent. Chromatographic purifications were carried out using flash grade silica gel (SDS Chromatogel 60 ACC, 40-63 mm), neutral aluminium oxide (SDS, 63-200 μm) or basic aluminium oxide (SDS, 50-200 μm). Organic solutions were concentrated under reduced pressure on a Büchi rotary evaporator.

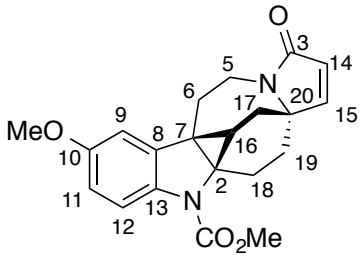
NMR spectra were recorded at 298 K (unless otherwise stated) on a Bruker Avance 300, Bruker Avance 400 Ultrashield and Bruker Avance 500 Ultrashield apparatuses. The signals are given as d / ppm (multiplicity, coupling constant (Hertz), number of protons) downfield from tetramethylsilane, with calibration on the residual protio-solvent used (d_H = 7.27 ppm and d_C = 77 ppm for $CDCl_3$, d_H = 5.32 ppm and d_C = 53.84 ppm for CD_2Cl_2). Mass spectra were recorded on a Waters Micromass LCT Premier (ESI), Waters Micromass GCT (EI, CI) and Bruker Daltonics Autoflex (MALDI) spectrometers. Melting points were determined using a Büchi melting point apparatus.

Crystal structure determinations were carried out using a Bruker-Nonius diffractomer equipped with an APPEX 2 4K CCD area detector, a FR591 rotating anode with MoK_a radiation, Montel mirrors as monochromator and a Kryoflex low temperature device (T = –173 ºC). Full-sphere data collection was used with w and j scans. *Programs used*: Data collection APEX-2, data reduction Bruker Saint V/.60A and absorption correction SADABS. Structure Solution and Refinement: Crystal structure solutions were achieved using direct methods as implement in SHELXTL and visualized using the program XP. Missing atoms were subsequently located from difference Fourier synthesis and added to the atom list. Least-squares refinement on F2 using all measured intensities was carried out using the program SHELXTL. All non-hydrogen atoms were refined including anisotropic displacement parameters.

HPLC analysis was carried out on an Agilent Technologies instrument HPLC 1100 series with VWD detector or HPLC 1200 series with DAD detector.

All reagents were used as purchased and used with no further purification, unless otherwise stated.

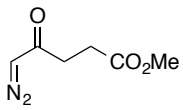
The nomenclature of the compounds followed the names as given by ChemDraw however for practical reasons, we decided to use the numbering as defined in the initial isolation report to compare the NMR data of our synthetic lundurines and the ones previously described, this numbering is depicted below.



Experimental procedures and characterization for the total synthesis of lundurines A–C

1. Intermediates in the synthesis of tetracycle 93a

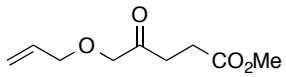
Methyl 5-diazo-4-oxopentanoate (81)



In a dry 2-neck round-bottom flask, methyl 4-chloro-4-oxobutyrate (15.4 mL, 125 mmol, 1 equiv) was diluted with acetonitrile (HPLC grade, 300 mL), the solution placed under argon and (trimethylsilyl)diazomethane (2M in diethyl ether, 100 mL, 200 mmol, 1.6 equiv) was added slowly dropwise so as to maintain the temperature of the reaction below 35 ºC. After addition, the solution was stirred at 25 ºC for 4 h. The volatiles were removed under reduced pressure (temperature < 35 ºC) and the residue loaded on silica gel column and purified by chromatography eluting with cyclohexane/EtOAc 4 : 1 to 1 : 3 to afford the title product as a yellow oil (15.6 g, 100 mmol, yield = 80%).

^{1}H NMR (300 MHz, $CDCl_3$) δ 5.31 (br s, 1H), 3.66 (s, 3H), 2.63 (br s, 4H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 192.5, 172.6, 54.2, 51.4, 34.6, 28.1. **HRMS** (ESI+) *m/z* calc. for $C_6H_8N_2O_3Na^+$ $[M+Na]^+$: 179.0427, found: 179.0425.

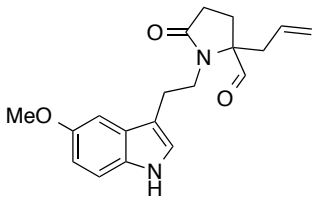
Methyl 5-(allyloxy)-4-oxopentanoate (74a)



Indium (III) triflate (360 mg, 0.64 mmol, 2 mol %) was dissolved in allyl alcohol (11 mL, *ca.* 5 equiv) in an oven-dried flask under argon atmosphere and the solution was cooled at 0 ºC. Methyl 5-diazo-4-oxopentanoate **81** (5.0 g, 32 mmol, 1 equiv) was slowly added via syringe pump (over 30 min) at 0 ºC. The resulting mixture was allowed to warm slowly to 25 ºC (over 1 h) and stirred for a further 1 h at 25 ºC. The volatiles were removed *in vacuo* and the resulting residue purified by column chromatography on silica gel eluting with pentane/Et_2O 4 : 1 to 1 : 1 to afford the title product as a colourless oil (3.90 g, 20.9 mmol, yield = 65%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.93 (ddt, *J* = 17.2, 10.5, 5.7 Hz, 1H), 5.33 (dq, *J* = 17.2, 1.5 Hz, 1H), 5.25 (dq, *J* = 10.4, 1.4 Hz, 1H), 4.11 (s, 2H), 4.08 (dt, *J* = 5.7, 1.4 Hz, 2H), 3.69 (s, 3H), 2.81 (t, *J* = 6.5 Hz, 2H), 2.65 (t, *J* = 6.5 Hz, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 207.3, 173.1, 133.7, 118.0, 75.0, 72.4, 51.8, 33.6, 27.3. **HRMS** (ESI+) *m/z* calc. for $C_9H_{14}O_4Na^+$ $[M+Na]^+$: 209.0784, found: 209.0783.

(±)-2-Allyl-1-(2-(5-methoxy-1*H*-indol-3-yl)ethyl)-5-oxopyrrolidine-2-carbaldehyde ((±)-75a)

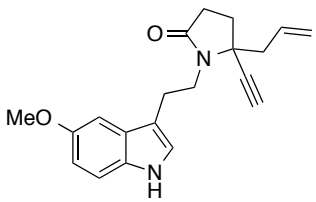


5-Methoxytryptamine (1.00 g, 5.26 mmol, 1 equiv) and methyl 5-(allyloxy)-4-oxopentanoate **74a** (1.03 g, 5.53 mmol, 1.05 equiv) were placed in a 2-neck 100 mL round-bottom flask equipped with a Dean-Stark apparatus and dissolved in a mixture of anhydrous pyridine / toluene 1 : 2 (15 mL : 30 mL). The resulting mixture was heated at 130 ºC for 40 h, then allowed to cool to room temperature and the solvents evaporated. The resulting crude mixture was dissolved in EtOAc (40 mL) and washed with a solution 1 M of HCl (30 mL). The aqueous layer was extracted with EtOAc (30 mL) and the combined organic layers were washed with water (2 × 30 mL) and brine (30 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The title product was obtained after flash chromatography (cyclohexane/EtOAc 7 : 3 to EtOAc) as a brown gum (1.27 g, 3.89 mmol, yield = 74%).

Note: Traces of 5-methoxytryptamine inhibit the next reaction. If they are observed by TLC, a second chromatography has to be carried out.

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.23 (s, 1H), 7.93 (br s, 1H), 7.24 (dd, *J* = 8.8, 0.6 Hz, 1H), 7.13 (d, *J* = 2.4 Hz, 1H), 7.01 (d, *J* = 2.4 Hz, 1H), 6.86 (dd, *J* = 8.8, 2.4 Hz, 1H), 5.72 – 5.60 (m, 1H), 5.26 – 5.15 (m, 2H), 3.89 (s, 3H), 3.67 (ddd, *J* = 13.8, 9.1, 6.4 Hz, 1H), 3.33 – 3.24 (m, 1H), 3.07 – 2.98 (m, 2H), 2.51 (d, *J* = 7.7 Hz, 2H), 2.49 – 2.42 (m, 2H), 2.12 – 1.94 (m, 2H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 198.8, 176.1, 154.1, 131.2, 130.4, 127.7, 122.7, 120.9, 112.6, 112.5, 111.9, 100.3, 71.7, 55.9, 42.1, 35.9, 29.3, 24.8, 24.1. **HRMS** (ESI–) *m/z* calc. for $C_{19}H_{21}N_2O_3^-$ $[M–H]^-$: 325.1558, found: 325.1559.

(±)-5-Allyl-5-ethynyl-1-(2-(5-methoxy-1*H*-indol-3-yl)ethyl)pyrrolidin-2-one ((±)-78a)

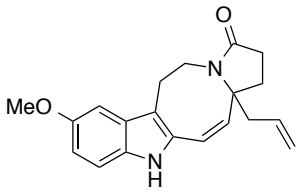


K_2CO_3 (906 mg, 6.56 mmol, 2 equiv) was added to a solution of (±)-7**5a** (1.07 g, 3.28 mmol, 1 equiv) in methanol (HPLC grade, 17 mL) and Bestmann-Ohira reagent (724 mg, 3.77 mmol, 1.15 equiv) was added slowly dropwise at 25 ºC as a solution in MeOH (3 mL). The mixture was stirred at 25 ºC for 3.5 h, then the volatiles were evaporated and the resulting crude mixture was suspended in the minimum amount of CH_2Cl_2 and purified by column chromatography on silica gel eluting with

cyclohexane/EtOAc 1 : 1 to 1 : 3 to afford the title compound as a colorless solid (927 mg, 2.26 mmol, yield = 88%).

M.p. 100-103 ºC. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.97 (br s, 1H), 7.30 – 7.24 (m, 2H), 7.08 (d, *J* = 2.4 Hz, 1H), 6.88 (dd, *J* = 8.7, 2.4 Hz, 1H), 5.82 (ddt, *J* = 16.7, 10.5, 7.2 Hz, 1H), 5.26 – 5.19 (m, 2H), 3.91 (s, 3H), 3.63 (ddd, *J* = 13.8, 11.0, 6.0 Hz, 1H), 3.55 (ddd, *J* = 13.8, 11.1, 5.2 Hz, 1H), 3.21 (ddd, *J* = 13.8, 11.1, 5.2 Hz, 1H), 3.11 (ddd, *J* = 13.9, 11.1, 6.0 Hz, 1H), 2.65 (ddt, *J* = 13.8, 6.9, 1.3 Hz, 1H), 2.57 – 2.49 (m, 2H), 2.47 – 2.40 (m, 2H), 2.30 (ddd, *J* = 12.9, 9.7, 6.2 Hz, 1H), 2.22 – 2.15 (m, 1H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 174.7, 153.9, 131.4, 131.4, 127.8, 122.7, 120.1, 113.0, 112.2, 111.9, 100.7, 84.7, 73.1, 60.5, 55.9, 44.1, 41.9, 31.7, 29.5, 24.5. **HRMS** (ESI+) *m*/*z* calc. for $C_{20}H_{22}N_2O_2Na^+$ $[M+Na]^+$: 345.1573, found: 345.1582.

(±)-(*Z*)-13a-Allyl-8-methoxy-1,2,5,6,11,13a-hexahydro-3*H*-pyrrolo[1',2':1,8]azocino[5,4-*b*]indol-3-one ((±)-93a)



In the glovebox, AuCl (54 mg, 0.23 mmol, 5 mol %) was added to a solution of (±)-**78a** (1.50 g, 4.65 mmol, 1 equiv) in anhydrous CH_2Cl_2 (3 mL) placed in a screw-cap vial. The mixture was stirred at 25 ºC for 5 h (monitored by TLC, full conversion) upon which time the product precipitated. The reaction was filtered through a short pad of silica gel washing thoroughly with ethyl acetate (*ca.* 400 mL). The volatiles were removed under vacuum until *ca.* 70 mL of solvent remained and pentane (*ca.* 120 mL) was added. The precipitated solid was filtered off and dried under high vacuum to obtain the title product as a white solid (1.24 g, 3.85 mmol, yield = 83%).

Note 1: the next step (methoxycarbonyl protection) was carried out on the material obtained after filtration over silica.

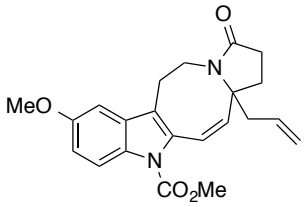
Note 2: alternatively, $IPrAu(NCMe)SbF_6$ (5 mol %) may be used as catalyst to give the title product in 95% yield (0.62 mmol scale). On this scale, the reaction with AuCl only required 5 mol % of catalyst to give 89% yield of tetracycle.

The structure of this compound was unambiguously confirmed by single crystal X-ray crystallography analysis (see below for more details). Solvent system for crystallization: dichloromethane, pentane.

M.p. 196-198 ºC. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.83 (br s, 1H), 7.10 (d, *J* = 8.7 Hz, 1H), 6.98 (d, *J* = 2.4 Hz, 1H), 6.79 (dd, *J* = 8.7, 2.4 Hz, 1H), 6.31 (d, *J* = 12.4 Hz, 1H),

5.91 – 5.79 (m, 1H), 5.51 (d, *J* = 12.4 Hz, 1H), 5.32 – 5.23 (m, 2H), 4.18 – 4.07 (m, 1H), 3.87 (s, 3H), 3.14 – 3.06 (m, 2H), 2.78 – 2.57 (m, 3H), 2.30 – 1.99 (m, 3H), 1.90 (ddd, *J* = 12.2, 8.1, 1.6 Hz, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 174.9, 154.1, 133.3, 132.5, 131.5, 131.4, 127.8, 119.9, 117.6, 112.7, 111.3, 110.6, 100.1, 66.2, 55.7, 43.6, 37.5, 33.7, 29.0, 22.5. **HRMS** (ESI+) *m/z* calc. for $C_{20}H_{23}N_2O_2^+$ $[M+H]^+$: 323.1754, found: 323.1750.

(±)-Methyl (*Z*)-13a-allyl-8-methoxy-3-oxo-1,2,3,5,6,13a-hexahydro-11*H*-pyrrolo[1',2':1,8]azocino[5,4-*b*]indole-11-carboxylate ((±)-94a)



A solution of NaHMDS (1.0 M in THF, 10.1 mL, 10.1 mmol, 1.5 equiv) was added to a solution of (±)-**93a** (2.16 g, 6.71 mmol, 1 equiv) in anhydrous THF (67 mL) at 0 ºC under argon atmosphere. After stirring at 0 ºC for 30 min, methyl chloroformate (0.8 mL, 10.36 mmol, 1.55 equiv) was slowly added and the resulting mixture was allowed to warm to 25 ºC and stirred for 1 h. Then the mixture was quenched by addition of a saturated aqueous solution of NH_4Cl (50 mL), diluted with EtOAc (100 mL) and brine (50 mL). The aqueous layer was extracted with EtOAc (2 × 100 mL) and the combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification by flash chromatography eluting with cyclohexane/EtOAc 1 : 1 to 3 : 7 gave the title product as a white solid (2.02 g, 5.32 mmol, yield = 80%).

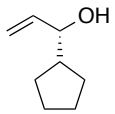
M.p. 153-155 ºC. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.88 (d, *J* = 9.0 Hz, 1H), 6.96 (d, *J* = 2.5 Hz, 1H), 6.88 (dd, *J* = 9.0, 2.6 Hz, 1H), 6.57 (d, *J* = 12.4 Hz, 1H), 5.84 (dddd, *J* = 16.7, 10.2, 7.8, 6.3 Hz, 1H), 5.54 (d, *J* = 12.4 Hz, 1H), 5.30 – 5.24 (m, 2H), 4.07 – 3.99 (m, 4H), 3.88 (s, 3H), 3.05 (dd, *J* = 13.6, 5.3 Hz, 1H), 2.97 (ddd, *J* = 14.0, 4.5, 1.7 Hz, 1H), 2.68 – 2.58 (m, 3H), 2.34 (ddd, *J* = 16.0, 11.9, 8.4 Hz, 1H), 2.12 (ddt, *J* = 16.0, 8.1, 1.1 Hz, 1H), 2.02 (td, *J* = 11.8, 8.0 Hz, 1H), 1.94 (ddd, *J* = 12.1, 8.4, 1.0 Hz, 1H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 175.3, 156.2, 152.3, 134.3, 131.4, 130.8, 130.5, 129.8, 120.0, 119.3, 117.3, 116.5, 113.3, 100.9, 65.7, 55.6, 53.4, 43.4, 36.2, 33.2, 28.9, 22.3. **HRMS** (ESI+) *m/z* calc. for $C_{22}H_{24}N_2O_4Na^+$ $[M+Na]^+$: 403.1628, found: 403.1629.

2. Synthesis of enantiopure alcohol (*S*)-79f and oxoester (*S*)-74f

(±)-1-cyclopentylprop-2-en-1-ol ((±)-**79f**) was prepared according to the literature.[57]

(–)-(*S*)-1-cyclopentylprop-2-en-1-ol ((–)-(*S*)-79f)

Resolution of the racemic chiral alcohol *via* enzymatic kinetic resolution[41]



In a dry 1L round-bottom flask under argon, powdered 4Å molecular sieves (4.3 g) were activated by heating (heat gun) under high vacuum (*ca.* 0.1 mbar) for 10 min. The flask was allowed to cool to room temperature under argon and novozyme 435 resin (930 mg, >5000 U/g) was added under argon. The solids were suspended in anhydrous toluene (350 mL) and isoprenyl acetate (21.8 mL, 198 mmol, *ca.* 4.55 equiv) was added immediately followed by addition of the racemic alcohol (±)-**79f** (5.5 g, 43.6 mmol, 1 equiv) in anhydrous toluene (10 mL). The resulting suspension was stirred vigorously and heated at 40 ºC for 40 h. The mixture was then loaded on silica gel column (*ca.* 500 g of silica gel pre-packed with pentane/diethyl ether 95 : 5) and purified by chromatography eluting with pentane/diethyl ether 95 : 5 to 3 : 1 to afford the enantiopure alcohol as a colourless oil (2.4 g, 19 mmol, yield = 44%) and the corresponding opposite enantiomer's acetate as a colourless liquid (3.3 g, 19.6 mmol, yield = 45%). Spectral data in agreement with the ones previously reported.

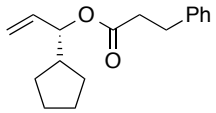
^{1}H NMR (500 MHz, $CDCl_3$) δ 5.84 (ddd, *J* = 17.0, 10.4, 6.5 Hz, 1H), 5.20 – 5.15 (m, 1H), 5.07 (dq, *J* = 10.6, 1.1 Hz, 1H), 3.84 (tt, *J* = 6.5, 1.2 Hz, 1H), 2.12 – 2.04 (m, 1H), 1.92 (sextet, *J* = 8.0 Hz, 1H), 1.79 – 1.71 (m, 1H), 1.64 – 1.44 (m, 5H), 1.40 – 1.31 (m, 1H), 1.26 – 1.17 (m, 1H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 140.4, 114.7, 77.1, 45.6, 28.7, 28.6, 25.5, 25.5.

Optical rotation in agreement with previous report for (*S*)-alcohol [α_D^{589} ($CHCl_3$, *c* 0.92, 294 K) = – 2.0 deg.cm^2.g^{-1}, 94% *ee*][58], measured α_D^{589} ($CHCl_3$, *c* 1.15, 302 K) = – 4.9 deg.cm^2.g^{-1}, >99% *ee*.

(57) Lafrance, M.; Roggen, M.; Carreira, E. M., *Angew. Chem. Int. Ed.* **2012**, *51*, 3470–3473.
(58) Wada, R.; Shibuguchi, T.; Makino, S.; Oisaki, K.; Kanai, M.; Shibasaki, M., *J. Am. Chem. Soc.* **2006**, *128*, 7687–7691.

Determination of enantiopurity:

(*S*)-1-cyclopentylallyl 3-phenylpropanoate ((*S*)-S1)



Alcohol **79f** (20 mg, 0.158 mmol, 1 equiv) was dissolved in CH_2Cl_2 (1 mL) and triethylamine (33 µL, 0.238 mmol, 1.5 equiv) and a crystal of DMAP were added, followed by addition of dihydrocinnamic acid anhydride[59] (49 mg, 0.174 mmol, 1.1 equiv). The mixture was stirred at 25 ºC for 1 h upon which time the alcohol had been fully consumed (TLC). The mixture was purified by chromatography on silica gel eluting with pentane/diethyl ether 98 : 2 to 95 : 5 to afford 35 mg of colourless oil (85%).

Note: same procedure applied to (±)-**79f** and (–)-(*S*)-**79f**.

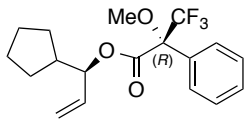
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.33 – 7.26 (m, 2H), 7.24 – 7.17 (m, 3H), 5.22 (ddd, *J* = 17.2, 10.5, 6.7 Hz, 1H), 5.23 – 5.10 (m, 3H), 2.99 (t, *J* = 7.8 Hz, 2H), 2.69 – 2.62 (m, 2H), 2.08 (sextet, *J* = 8.1 Hz, 1H), 1.73 – 1.47 (m, 6H), 1.33 – 1.17 (m, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 172.2, 140.5, 135.8, 128.4, 128.3, 126.2, 117.0, 78.4, 43.4, 36.1, 31.0, 28.7, 28.6, 25.5, 25.3. **HRMS** (ESI+) *m/z* calc. for $C_{17}H_{22}O_2Na^+$ $[M+Na]^+$: 281.1512, found: 281.1511. **α_D^{589}** ($CHCl_3$, *c* 1.25, 302 K) = – 0.5 deg.cm^2.g^{-1}. **SFC** (ChiralPack IE (150 × 3mm), CO_2/MeCN 97:3, 2 mL/min, 35 ºC, ABRP pressure 2000 psi) t_R (*major*) 2.34 min, t_R (*minor*) 2.60 min, >99% *ee*.

Confirmation of enantiopurity and absolute configuration:

Both (*R*)- and (*S*)-Mosher ester derivatives of (*S*)-**79f** were prepared according to the literature.[42]

Note: to avoid any confusion, the reaction of (*R*)-α-methoxy-α-trifluoromethylphenylacetyl chloride gives the (*S*)-Mosher ester and the reaction of (*S*)-α-methoxy-α-trifluoromethylphenylacetyl chloride gives the (*R*)-Mosher ester.

(*S*)-1-cyclopentylallyl (*R*)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoate ((*S*,*R*)-80f)



(*S*,*R*)-**80f** shows shielding of the cyclopentyl C***H*** and unshielding of the vinyl C***H*** compared to (*S*,*S*)-**80f**, this is consistent with the *S* configuration of the alcohol From (*S*)-α-methoxy-α-

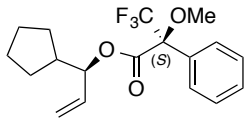
(59) Prepared according to Sheikh, M. C.; Takagi, S.; Yoshimura, T.; Morita, H., *Tetrahedron* **2010**, *66*, 7272–7278.

trifluoromethylphenylacetyl chloride and (*S*)-**79f**, obtained as a colourless solid with low melting point.

The structure of this compound was unambiguously confirmed by single crystal X-ray crystallography analysis (see below for more details). Solvent system for crystallization: hot pentane, then low temperature.

M.p. (pentane) 39-40 °C. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.57 – 7.51 (m, 2H), 7.43 – 7.37 (m, 3H), 5.83 (ddd, J = 17.1, 10.4, 7.7 Hz, 1H), 5.38 (dt, J = 17.2, 1.1 Hz, 1H), 5.34 (t, J = 7.8 Hz, 1H), 5.29 (dt, J = 10.4, 0.9 Hz, 1H), 3.56 (q, J_{H-P} = 1.2 Hz, 3H), 2.16 (sextet, J = 8.2 Hz, 1H), 1.68 – 1.46 (m, 6H), 1.29 – 1.17 (m, 2H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 165.9, 134.7, 132.5, 129.5, 128.3 (2C), 127.4 (app. d, J_{C-P} = 1.3 Hz, 2C), 123.4 (q, J_{C-P} = 288.5 Hz), 119.5, 84.4 (q, J_{C-P} = 27.6 Hz), 81.5, 55.4 (app. d, J_{C-P} = 1.4 Hz), 43.2, 28.7, 28.5, 25.4 (2C). **HRMS** (ESI+) *m/z* calc. for $C_{18}H_{21}O_3F_3Na^+$ $[M+Na]^+$: 365.1335, found: 365.1343. **α_D^{589}**($CHCl_3$, *c* 1.55, 299 K) = +36.6 deg.cm^2.g^{-1}.

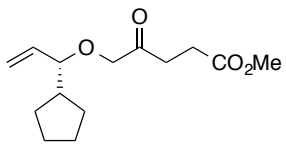
(*S*)-1-cyclopentylallyl (*S*)-3,3,3-trifluoro-2-methoxy-2-phenylpropanoate ((*S*,*S*)-80f)



From (*R*)-α-methoxy-α-trifluoromethylphenylacetyl chloride and (*S*)-**79f**, obtained as a pale yellow oil. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.56 – 7.50 (m, 2H), 7.43 – 7.37 (m, 3H), 5.72 (ddd, J = 17.5, 10.5, 7.3 Hz, 1H), 5.32 – 5.26 (m, 2H), 5.22 (dt, J = 10.4, 1.0 Hz, 1H), 3.57 (q, J_{H-P} = 1.3 Hz, 3H), 2.19 (sextet, J = 8.2 Hz, 1H), 1.83 – 1.75 (m, 1H), 1.73 – 1.50 (m, 5H), 1.39 – 1.22 (m, 2H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 165.9, 134.5, 132.4, 129.5, 128.3 (2C), 127.5 (app. d, J_{C-P} = 1.4 Hz, 2C), 123.4 (q, J_{C-P} = 288.5 Hz), 118.9, 84.6 (q, J_{C-P} = 27.5 Hz), 81.6, 55.5 (app. d, J_{C-P} = 1.5 Hz), 43.2, 29.1, 28.7, 25.5, 25.4. **HRMS** (ESI+) *m/z* calc. for $C_{18}H_{21}O_3F_3Na^+$ $[M+Na]^+$: 365.1335, found: 365.1361. **α_D^{589}** ($CHCl_3$, *c* 0.73, 298 K) = – 38.8 deg.cm^2.g^{-1}.

(*S*,*R*)-**80f** shows shielding of the cyclopentyl C***H*** and unshielding of the vinyl C***H*** compared to (*S*,*S*)-**80f**, this is consistent with the *S* configuration of the alcohol.[43]

(+)-Methyl (*S*)-5-(1-cyclopentylallyl)oxy)-4-oxopentanoate ((*S*)-74f)



Indium (III) triflate (97 mg, 0.173 mmol, 3 mol %) was placed in an oven-dried Schlenk tube under argon atmosphere. The tube was cooled at 0 ºC for 5 min and chiral alcohol (*S*)-**79f** (3.64 g, 28.8 mmol, 5 equiv) was added in one portion followed by slow dropwise addition of diazo compound methyl 5-diazo-4-oxopentanoate (900

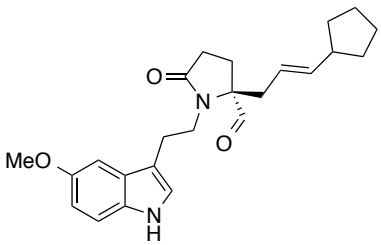
mg, 5.76 mmol, 1 equiv) over 1 h at 0 ºC. After addition, the mixture was stirred at 0 ºC for additional 30 min and then allowed to warm to 25 ºC and stirred until no effervescence was detected in the viscous reaction medium (typically 1–2 h). The mixture was then diluted with CH_2Cl_2 (5 mL) and filtered through a short plug of silica gel eluting with pentane/diethyl ether 3 : 1. The fractions containing the product (and unreacted alcohol) were collected and concentrated *in vacuo* (40 ºC, 550 mbars). The residue (pale yellow) was diluted with CH_2Cl_2 (10 mL) and Et_3N (8 mL, 10 equiv) was added followed by addition of a crystal of DMAP and acetic anhydride (4 mL, 7.5 equiv) dropwise at 25 ºC. The resulting mixture was stirred at 25 ºC for 1 h and then immediately loaded on silica gel column and purified by chromatography eluting with pentane/diethyl ether 98:2 to 3:1 to afford a colourless oil (650 mg, 2.53 mmol, yield = 44%, analytically pure ketoester) and the acetylated chiral alcohol. The latter was deprotected (recycled) by treatment with potassium carbonate (10.9 g, theor. 78.8 mmol, 3 equiv based on "unreacted" 4.56 equivalents of excess chiral alcohol) in 15 mL of methanol for 3 h at 25 ºC. The mixture was poured on 250 mL of brine and extracted with diethyl ether (100 mL + 3 × 70 mL). The combined ethereal layers were concentrated and the residue loaded on silica gel column and purified by chromatography eluting with pentane/diethyl ether 4 : 1 to 3 : 1 to afford a colourless oil (2.69 g, 21.27 mmol, yield = 81%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.64 (ddd, *J* = 17.1, 10.3, 8.3 Hz, 1H), 5.22 (ddd, *J* = 10.3, 1.8, 0.6 Hz, 1H), 5.16 (ddd, *J* = 17.2, 1.8, 0.7 Hz, 1H), 4.09 (d, *J* = 17.0 Hz, 1H), 3.91 (d, *J* = 17.0 Hz, 1H), 3.67 (s, 3H), 3.46 (t, *J* = 8.0 Hz, 1H), 2.81 (t, *J* = 6.8 Hz, 2H), 2.59 (t, *J* = 6.8 Hz, 2H), 2.04 (sextet, *J* = 8.0 Hz, 1H), 1.90 – 1.76 (m, 1H), 1.68 – 1.38 (m, 6H), 1.29 – 1.16 (m, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 208.0, 173.1, 137.2, 118.5, 86.6, 73.5, 51.7, 44.2, 33.9, 29.1, 28.7, 27.2, 25.5, 25.4. **HRMS** (ESI+) *m/z* calc. for $C_{14}H_{22}O_4Na^+$ $[M+Na]^+$: 277.1410, found: 277.1414. $\boldsymbol{\alpha_D^{589}}$ ($CHCl_3$, *c* 1.05, 300 K) = + 36.2 deg.cm^2.g^{-1}; >99% *ee*.

<u>*Note:*</u> the enantiopurity of this compound was not measured by HPLC since it presented no chromophore, however, by analogy with derivatives bearing an arene instead of the cyclopentyl substituent, we know that the reaction between the diazo compound and chiral alcohols in the presence of $In(OTf)_3$ does not suffer any racemization.

3. Racemic and asymmetric total synthesis of lundurine C

(–)-(*S*,*E*)-2-(3-Cyclopentylallyl)-1-(2-(5-methoxy-1*H*-indol-3-yl)ethyl)-5-oxopyrrolidine-2-carbaldehyde ((–)-(*S*,*E*)-75f)



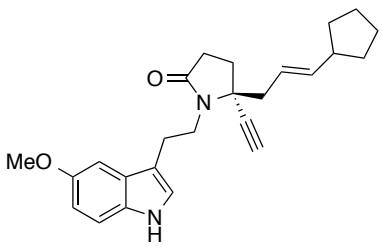
In a dry 25 mL round-bottom flask, 5-methoxytryptamine (800 mg, 4.2 mmol, 1.92 equiv) was suspended in triethylamine (8 mL) and methyl (*S*)-5-(cyclopentylally)loxy)-4-oxopentanoate (**75f**) (95% purity, 556 mg, 2.19 mmol, 1 equiv) was added as a solution in toluene (4 mL). The flask was equipped with a Dean-Stark apparatus and the mixture heated at 105 ºC (reflux) for 16 h, then cooled to room temperature and the solvents evaporated. The resulting crude oil was dissolved in EtOAc (15 mL) and 0.5 M of HCl (10 mL) was added and the biphasic mixture stirred vigorously at 25 ºC for 20 min. The organic layer was collected and the aqueous layer was re-extracted with EtOAc (2 × 20 mL). The combined organic layers were washed with 0.5 M of HCl (2 × 15 mL), dried over Na_2SO_4 and concentrated under reduced pressure. The title product was obtained after column chromatography on silica gel eluting with cyclohexane/EtOAc 1 : 1 to 1 : 4 as a pale brown gum (730 mg, 1.85 mmol, yield = 84%).

Note: the aldehyde is isolated as an unseparable 12 : 1 mixture of two compounds that seem isomeric and are presumably the *E* and *Z*-olefin isomers. The NMR data given below are for the major *E* isomer. The optical rotation was measured on the mixture.

^{1}H NMR (500 MHz, $CDCl_3$) δ 9.25 (s, 1H), 8.24 (br s, 1H), 7.24 (d, *J* = 8.8 Hz, 1H), 7.14 (d, *J* = 2.5 Hz, 1H), 6.99 (d, *J* = 2.4 Hz, 1H), 6.85 (dd, *J* = 8.8, 2.4 Hz, 1H), 5.57 (ddt, *J* = 15.2, 7.7, 1.3 Hz, 1H), 5.23 (dtd, *J* = 15.5, 7.3, 1.1 Hz, 1H), 3.89 (s, 3H), 3.71 – 3.60 (m, 1H), 3.35 – 3.23 (m, 1H), 3.07 – 2.99 (m, 2H), 2.48 – 2.39 (m, 5H), 2.07 – 1.93 (m, 2H), 1.81 – 1.49 (m, 6H), 1.30 – 1.18 (m, 2H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 199.3, 176.2, 154.1, 141.9, 131.2, 127.8, 122.7, 119.3, 112.6, 112.6, 111.9, 100.3, 72.1, 55.8, 43.3, 42.1 (2C), 34.6, 33.0, 32.9, 29.4, 25.1, 24.8, 24.0. **HRMS** (ESI–) *m/z* calc. for $C_{24}H_{29}N_2O_3^-$ $[M–H]^-$: 393.2184, found: 393.2196. $\boldsymbol{\alpha_D^{589}}$ ($CHCl_3$, *c* 1.0, 300 K) = –39.3 deg.cm^2.g^{-1}; 78% *ee*.

Note: unstable on HPLC.

(+)-(*S*,*E*)-5-(3-Cyclopentylallyl)-5-ethynyl-1-(2-(5-methoxy-*1H*-indol-3-yl)ethyl)pyrrolidin-2-one ((+)-(*S*,*E*)-78f)

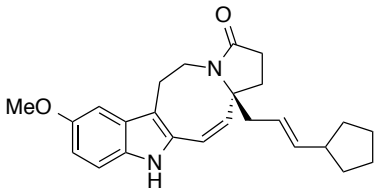


K_2CO_3 (575 mg, 4.16 mmol, 2 equiv) was added to a solution of (–)-(*S*,*E*)-**78f** (820 mg, 2.08 mmol, 1 equiv) in methanol (6 mL) at 25 ºC and Bestmann-Ohira reagent (459 mg, 2.39 mmol, 1.15 equiv) in methanol (2 mL) was added dropwise at 25 ºC. The mixture was stirred at 25 ºC for 4 h. The volatiles were evaporated and the resulting crude material was partitioned between CH_2Cl_2 (15 mL) and saturated aqueous ammonium chloride (10 mL). The organic layer was collected and the aqueous phase extracted with CH_2Cl_2 (2 × 15 mL). The combined organic layers were concentrated and the resulting crude oil purified by column chromatography on silica gel eluting with cyclohexane/EtOAc 2 : 1 to 3 : 2 to afford the title compound as pale yellow solid (681 mg, 1.74 mmol, yield = 84%).

Note: also isolated as an unseparable 12 : 1 mixture of presumed *E* and *Z*-olefin isomers. The NMR data given below are for the major *E* isomer. The solid was crystallized from CH_2Cl_2/pentane and the optical rotation and melting point were measured on the crystalline material (82% *ee*).

M.p. (CH_2Cl_2/pentane) 153-155 °C (82% *ee*). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.03 (br s, 1H), 7.27 – 7.24 (m, 2H), 7.05 (d, *J* = 2.4 Hz, 1H), 6.86 (dd, *J* = 8.8, 2.4 Hz, 1H), 5.56 (ddt, *J* = 15.4, 7.6, 1.2 Hz, 1H), 5.35 (dtd, *J* = 15.3, 7.2, 1.1 Hz, 1H), 3.89 (s, 3H), 3.62 (ddd, *J* = 13.7, 11.1, 5.9 Hz, 1H), 3.51 (ddd, *J* = 13.8, 11.3, 5.1 Hz, 1H), 3.19 (ddd, *J* = 13.5, 11.4, 5.1 Hz, 1H), 3.10 (ddd, *J* = 13.8, 11.2, 5.9 Hz, 1H), 2.58 – 2.36 (m, 6H), 2.26 (ddd, *J* = 12.8, 9.7, 6.5 Hz, 1H), 2.17 (ddd, *J* = 12.9, 9.3, 6.5 Hz, 1H), 1.81 – 1.71 (m, 2H), 1.69 – 1.49 (m, 4H), 1.31 – 1.21 (m, 2H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 174.7, 153.9, 141.3, 131.4, 127.9, 122.7, 120.4, 113.2, 112.2, 111.8, 100.8, 85.2, 72.9, 60.8, 55.9, 43.3, 42.9, 41.8, 33.0 (2C), 31.5, 29.6, 25.1 (2C), 24.5. **HRMS** (ESI+) *m*/*z* calc. for $C_{25}H_{30}N_2O_2Na^+$ $[M+Na]^+$: 413.2199, found: 413.2208. **HPLC** (Chiralpak IA (250 mm × 4.6 mm), hexane/isopropanol 80 : 20, 1 mL/min) t_R (*major*) 8.0 – 8.1 min, t_R (*minor*) 8.9 – 9.0 min, 77–78% *ee*. $\boldsymbol{\alpha_D^{589}}$ ($CHCl_3$, *c* 0.49, 302 K) = + 4.2 deg.cm^2.g^{-1}; 82% *ee*.

(+)-(*S*,*Z*)-13a-((*E*)-3-Cyclopentylallyl)-8-methoxy-1,2,5,6,11,13a-hexahydro-3*H*-pyrrolo[1',2':1,8]azocino[5,4-*b*]indol-3-one ((+)-(*S*,*Z*,*E*)-93f)

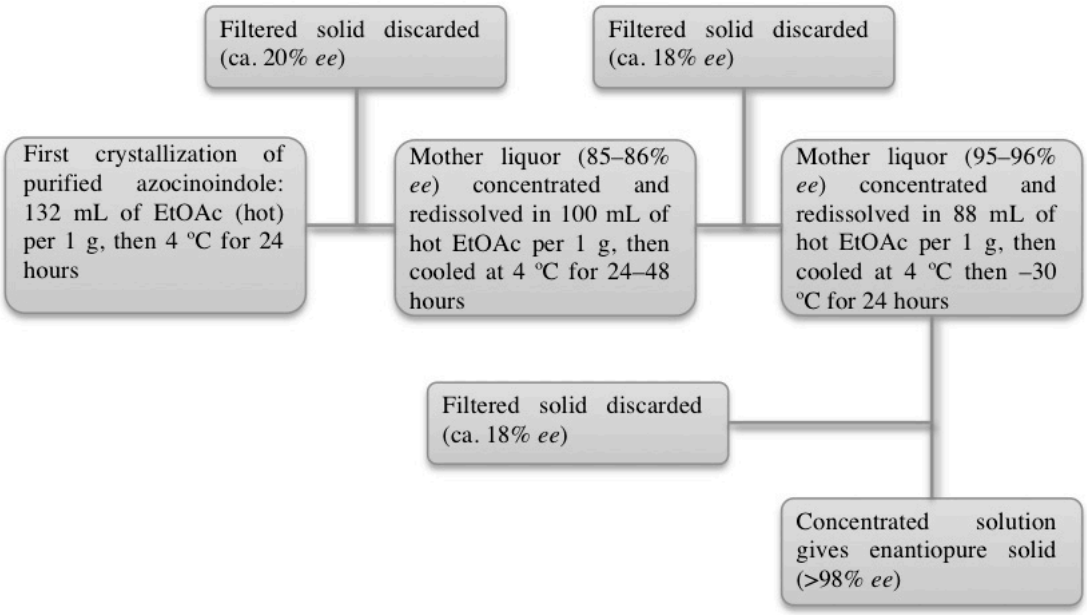


In the glovebox, AuCl (15 mg, 0.065 mmol, 8 mol %) was added to a suspension of (+)-(*S*,*E*)-**78f** (320 mg, 0.82 mmol, 1 equiv) in anhydrous CH_2Cl_2 (1 mL). After 5 h stirring at 25 ºC, the reaction mixture was loaded on silica gel column and purified by chromatography eluting with cyclohexane/EtOAc 3 : 1 to 1 : 1 to afford an off-white solid (254 mg, 0.65 mmol, yield = 79%, 77–78% *ee*).

Note: isolated as an unseparable 12 : 1 mixture of presumed *E* and *Z*-olefin isomers. The NMR data given below are for the major *E* isomer. The optical rotation and melting point were measured on the solid obtained after crystallization (see below).

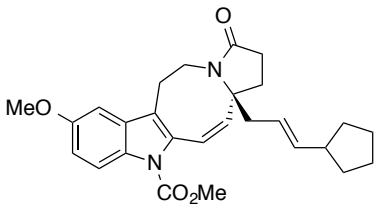
Crystallization to enantiopurity (2–3 crystallizations):

The purified solid (380 mg) was dissolved in 50 mL of hot ethyl acetate and the solution left to cool to room temperature then placed in the fridge (4 ºC) for 24 h. The solution was collected by filtration through a teflon filter and showed 85–86% *ee* (20–21% *ee* for the solid that was discarded). The solvent was removed *in vacuo* and the remaining solid (310 mg) was redissolved in 30 mL of hot ethyl acetate and the solution left to cool to room temperature and then cooled at 4 ºC for 24–48 h (slow crystallization). The solution was collected *via* filtration through a teflon filter and presented 95–96% *ee* (18% *ee* for the solid that was discarded). The solvent was removed *in vacuo* and a third crystallization was performed on the remaining solid (285 mg) dissolving in 25 mL of hot ethyl acetate, leaving to cool to room temperature, then cooling at 4 ºC and finally –30 ºC for 24 h. The solution then collected showed >98% *ee*, concentration of the solution afforded 271 mg of colourless solid (71% yield of crystallization, compound as *ca.* 12:1 mixture of presumed *E* and *Z* isomers); 56% yield over cyclization and 3 crystallizations.



M.p. 169-172 °C (20% *ee*), 87-89 °C (>98% *ee*). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.82 (br s, 1H), 7.11 (d, *J* = 8.7 Hz, 1H), 6.98 (d, *J* = 2.4 Hz, 1H), 6.80 (dd, *J* = 8.8, 2.4 Hz, 1H), 6.30 (d, *J* = 12.4 Hz, 1H), 5.64 (dd, *J* = 15.2, 7.7 Hz, 1H), 5.51 (d, *J* = 12.4 Hz, 1H), 5.42 (dtd, *J* = 15.2, 7.1, 1.0 Hz, 1H), 4.16 – 4.07 (m, 1H), 3.88 (s, 3H), 3.16 – 3.07 (m, 2H), 2.78 – 2.69 (m, 1H), 2.57 (d, *J* = 7.5 Hz, 2H), 2.48 (sextet, *J* = 8.0 Hz, 1H), 2.28 – 1.99 (m, 3H), 1.90 – 1.77 (m, 3H), 1.73 – 1.53 (m, 4H), 1.37 – 1.26 (m, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 175.1, 154.1, 140.9, 133.8, 132.6, 131.4, 127.8, 120.6, 117.3, 112.7, 111.3, 110.5, 100.1, 66.6, 55.8, 43.4, 42.3, 37.6, 33.6, 33.1, 33.1, 29.1, 25.1 (2C), 22.5. **HRMS** (ESI–) *m/z* calc. for $C_{25}H_{29}N_2O_2^-$ $[M–H]^-$: 389.2235, found: 389.2239. **HPLC** (Chiralpak IA (250 mm × 4.6 mm), hexane/THF/ethanol 92 : 5 : 3, 1 mL/min) t_R (*minor*) 24.9 – 25.3 min, t_R (*major*) 29.3 – 29.7 min. **α_D^{589}** ($CHCl_3$, *c* 1.05, 302 K) = + 133.3 deg.cm^2.g^{-1} (>98% *ee*).

(+)-Methyl (*S*,*Z*)-13a-((*E*)-3-cyclopentylallyl)-8-methoxy-3-oxo-1,2,3,5,6,13a-hexahydro-11*H*-pyrrolo[1',2':1,8]azocino[5,4-*b*]indole-11-carboxylate ((+)-(*S*,*Z*,*E*)-94f)

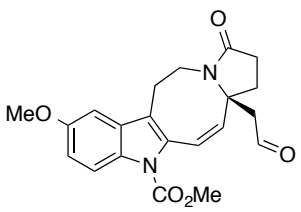


In a dry Schlenk flask under argon, diisopropylamine (56 µL, 0.394 mmol, 1.1 equiv) was diluted with anhydrous THF (2 mL) and the solution cooled to 0 ºC and *n*-BuLi (2.2M in cyclohexane, 179 µL, 0.394 mmol, 1.1 equiv) was added dropwise. The solution was left stirring at 0 ºC for 10 min and

min. After addition, the mixture was stirred for 30 min at 0 ºC and methyl chloroformate (29 µL, 0.376 mmol, 1.05 equiv) was added dropwise and the resulting mixture was stirred at 0 ºC for 15 min then allowed to warm to room temperature (25 ºC) slowly and stirred at 25 ºC for 1 h. The mixture was quenched by addition of saturated aqueous ammonium chloride (5 mL) and diluted with EtOAc (20 mL) and brine (20 mL). The aqueous layer was re-extracted with EtOAc (2 × 20 mL) and the combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification by column chromatography on silica gel eluting with diethyl ether gave the title product as a colourless solid (141 mg, 0.314 mmol, yield = 88%).

M.p. 78-80 ºC (>98% *ee*). **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.87 (d, *J* = 9.0 Hz, 1H), 6.94 (d, *J* = 2.5 Hz, 1H), 6.86 (dd, *J* = 9.0, 2.5 Hz, 1H), 6.54 (d, *J* = 12.3 Hz, 1H), 5.63 (dd, *J* = 15.2, 7.7 Hz, 1H), 5.52 (d, *J* = 12.4 Hz, 1H), 5.40 (dt, *J* = 14.7, 7.0 Hz, 1H), 4.05 – 3.94 (m, 4H), 3.86 (s, 3H), 3.06 (dd, *J* = 13.4, 5.2 Hz, 1H), 2.95 (dd, *J* = 14.0, 3.4 Hz, 1H), 2.62 (td, *J* = 13.8, 5.4 Hz, 1H), 2.54 (d, *J* = 7.0 Hz, 2H), 2.46 (sextet, *J* = 8.3 Hz, 1H), 2.31 (ddd, *J* = 15.8, 11.8, 8.3 Hz, 1H), 2.09 (dd, *J* = 16.0, 8.0 Hz, 1H), 2.04 – 1.94 (m, 1H), 1.89 (dd, *J* = 12.0, 8.2 Hz, 1H), 1.84 – 1.73 (m, 2H), 1.71 – 1.51 (m, 4H), 1.35 – 1.25 (m, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 175.4, 156.1, 152.2, 140.9, 134.3, 131.1, 130.4, 129.7, 120.5, 119.0, 117.1, 116.4, 113.2, 100.8, 66.0, 55.5, 53.3, 43.4, 42.1, 36.2, 33.1, 33.1, 33.0, 28.9, 25.1 (2C), 22.2. **HRMS** (ESI+) *m/z* calc. for $C_{27}H_{33}N_2O_4^+$ $[M+H]^+$: 449.2435, found: 449.2429. **α_D^{589}** ($CHCl_3$, *c* 1.04, 301 K) = +143.1 deg.cm^2.g^{-1} (>98% *ee*).

(±)-Methyl (*S*,*Z*)-8-methoxy-3-oxo-13a-(2-oxoethyl)-1,2,3,5,6,13a-hexahydro-11*H*-pyrrolo[1',2':1,8]azocino[5,4-*b*]indole-11-carboxylate ((±)-(*S*,*E*)-95)

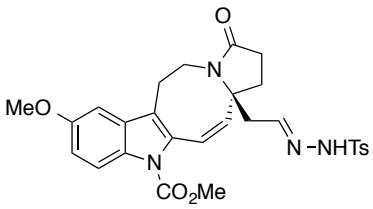


In a dry round-bottom flask, (±)-**94a** (200 mg, 0.526 mmol, 1 equiv) was dissolved in acetone (5 mL) and NMO (154 mg, 1.314 mmol, 2.5 equiv) and a freshly prepared solution of OsO_4 (5 mg/mL, 0.8 mL, 4 mg, 0.016 mmol, 3 mol %) were added. The mixture was stirred vigorously at 25 ºC until full consumption of the starting material (monitored by TLC, typically 6 h). The volatiles were then removed under vacuum at 25 ºC (water bath) and the remaining brown residue dried under high vacuum (≤ 0.1 mbar) for 20 min. It was then redissolved in acetone/water 2 : 1 (5 mL) and $NaIO_4$ (506 mg, 2.366 mmol, 4.5 equiv) was added in one portion to the vigorously

stirred solution. Stirring was continued for 30 min upon which time all diol had been converted to the aldehyde (monitored by TLC). The suspension was then poured on 100 mL of brine and extracted with EtOAc (3 × 70 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated *in vacuo* to give crude aldehyde, which was directly used is the following step without further purification.

^{1}H NMR (500 MHz, $CDCl_3$) δ 9.94 (t, *J* = 2.8 Hz, 1H), 7.91 (d, *J* = 9.0 Hz, 1H), 6.97 (d, *J* = 2.5 Hz, 1H), 6.92 (dd, *J* = 9.0, 2.6 Hz, 1H), 6.66 (d, *J* = 12.3 Hz, 1H), 5.65 (d, *J* = 12.3 Hz, 1H), 4.13 (td, *J* = 14.0, 13.6, 4.5 Hz, 1H), 4.03 (s, 3H), 3.90 (s, 3H), 3.05 (dd, *J* = 16.2, 2.5 Hz, 1H), 3.02 – 2.94 (m, 2H), 2.89 (dd, *J* = 16.2, 2.0 Hz, 1H), 2.66 (td, *J* = 13.8, 5.2 Hz, 1H), 2.43 (ddd, *J* = 15.9, 11.9, 8.1 Hz, 1H), 2.34 (dd, *J* = 12.0, 8.1 Hz, 1H), 2.22 (dd, *J* = 15.9, 8.0 Hz, 1H), 2.13 (td, *J* = 11.9, 8.2 Hz, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 198.6, 174.7, 156.3, 152.2, 133.8, 130.5, 129.6, 129.3, 120.5, 117.4, 116.5, 113.6, 100.9, 64.0, 55.6, 53.5, 51.9, 36.5, 34.7, 28.8, 22.4. **HRMS** (ESI+) *m/z* calc. for $C_{21}H_{22}N_2O_5Na^+$ $[M+Na]^+$: 405.1421. Found: 405.1404.

(±)-Methyl (*Z*)-8-methoxy-3-oxo-13a-((*E*)-2-(2-(*p*-toluenesulfonylhydrazono)ethyl)-1,2,3,5,6,13a-hexahydro-11*H*-pyrrolo[1',2':1,8]azocino[5,4-*b*]indole-11-carboxylate ((±)-(*Z*,*E*)-96)



The mixture was redissolved in CH_2Cl_2 (4 mL) and $TsNHNH_2$ (98 mg, 0.526 mmol, 1 equiv) was added followed by addition of a crystal of PTSA. The brown solution was stirred at 25 ºC for 5 min upon which time TLC showed full conversion of the aldehyde. The mixture was loaded on silica gel column and purified by chromatography eluting with cyclohexane/EtOAc 3 : 7 to 0 : 1 to afford the product as an off-white solid (220 mg, 0.40 mmol, *E* : *Z* = 100 : 7, yield from (±)-**94a** = 76%).

Note: the same procedure was applied on 740 mg of (±)-**94a** (1.85 mmol) yielding 930 mg of hydrazone (±)-(*Z*,*E*)-**96** (91%).

M.p. 202-204 ºC. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.61 (s, 1H), 7.89 (d, *J* = 9.0 Hz, 1H), 7.79 – 7.73 (m, 2H), 7.32 – 7.28 (m, 2H), 7.06 (t, *J* = 5.9 Hz, 1H), 6.94 (d, *J* = 2.5 Hz, 1H), 6.90 (dd, *J* = 9.0, 2.5 Hz, 1H), 6.52 (d, *J* = 12.3 Hz, 1H), 5.32 (d, *J* = 12.3 Hz, 1H), 4.02 (s, 3H), 3.90 – 3.81 (m, 4H), 2.89 – 2.81 (m, 2H), 2.77 – 2.67 (m, 2H), 2.50 (td, *J* = 13.9, 5.5 Hz, 1H), 2.44 (s, 3H), 2.28 (ddd, *J* = 16.3, 11.9, 8.3 Hz, 1H), 1.97 (dd, *J* =

16.4, 8.0 Hz, 1H), 1.84 (dd, *J* = 12.2, 8.2 Hz, 1H), 1.76 (td, *J* = 12.1, 8.1 Hz, 1H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 175.3, 156.2, 152.2, 145.8, 144.2, 135.3, 133.9, 130.5, 129.9, 129.6 (2C), 129.6, 127.9 (2C), 119.9, 117.2, 116.5, 113.4, 101.0, 65.3, 55.6, 53.5, 41.0, 36.3, 33.3, 28.7, 22.1, 21.6. **HRMS** (ESI–) *m/z* calc. for $C_{28}H_{29}N_4O_6S^-$ [M–H]$^-$: 549.1813, found: 549.1798.

(+)-Methyl (*S*,*Z*)-8-methoxy-3-oxo-13a-((*E*)-2-(2-(*p*-toluenesulfonylhydrazono)ethyl)-1,2,3,5,6,13a-hexahydro-11*H*-pyrrolo[1',2':1,8]azocino[5,4-*b*]indole-11-carboxylate ((+)-(*S*,*Z*,*E*)-96).

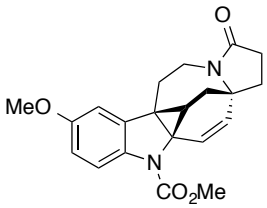
In a dry round-bottom flask, (+)-(*S*,*Z*,*E*)-**94f** (100 mg, 0.223 mmol) was dissolved in acetone (1 mL) and NMO (65 mg, 0.555 mmol, 2.5 equiv) and a freshly prepared solution of OsO_4 (5 mg/mL, 0.3 mL, 1.5 mg, 6.6 μmol, 3 mol %) were added. The mixture was stirred vigorously at 25 ºC until full consumption of the starting material (monitored by TLC, typically 1.5 h). The volatiles were then removed under vacuum at 25 ºC (water bath) and the remaining brown residue dried under high vacuum (≤ 0.1 mbar) for 20 min. It was then redissolved in acetone / water 2 : 1 (3 mL) and $NaIO_4$ (215 mg, 1.0 mmol, 4.5 equiv) was added in one portion to the vigorously stirred solution. Stirring was continued for 30 min upon which time all diol had been converted to the aldehyde (monitored by TLC). The suspension was then poured on 50 mL of brine and extracted with EtOAc (3 × 30 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated *in vacuo*. The residue was dried under high vacuum (≤ 0.1 mbar) for 30 min (to remove most of the volatile cyclopentanecarboxaldehyde).

The mixture was redissolved in CH_2Cl_2 (3 mL) and $TsNHNH_2$ (46 mg, 0.247 mmol, 1.1 equiv) was added followed by addition of a crystal of PTSA. The brown solution was stirred at 25 ºC for 10 min upon which time TLC showed full conversion of the aldehyde. The mixture was loaded on silica gel column and purified by chromatography eluting with cyclohexane/EtOAc 3 : 7 to 0 : 1 to afford the product as an off-white solid (97 mg, 0.176 mmol, *E* : *Z* = 100 : 7, yield from (+)-(*S*,*Z*,*E*)-**94f** = 79%).

The structure of this compound was unambiguously confirmed by single crystal X-ray crystallography analysis (see below for more details). Solvent system for crystallization: chloroform, pentane, and acetonitrile.

Analytical data identical to the ones of the racemic compound. **M.p.** 188-191 ºC (>98% *ee*). $\boldsymbol{\alpha_D^{589}}$ ($CHCl_3$, *c* 1.15, 301 K) = + 541.6 deg.cm^2.g^{-1}.

(±)-Methyl (5a*R,5b*S**,6a*S**,12a*R**)-2-methoxy-9-oxo-5b,6,8,9,11,12-hexahydro-5*H*,7*H*-5a,6a-ethenopyrrolo[1'',2'':1',7']azepino[4',5':2,3]cyclopropa[1,2-*b*]indole-5-carboxylate ((±)-48)**

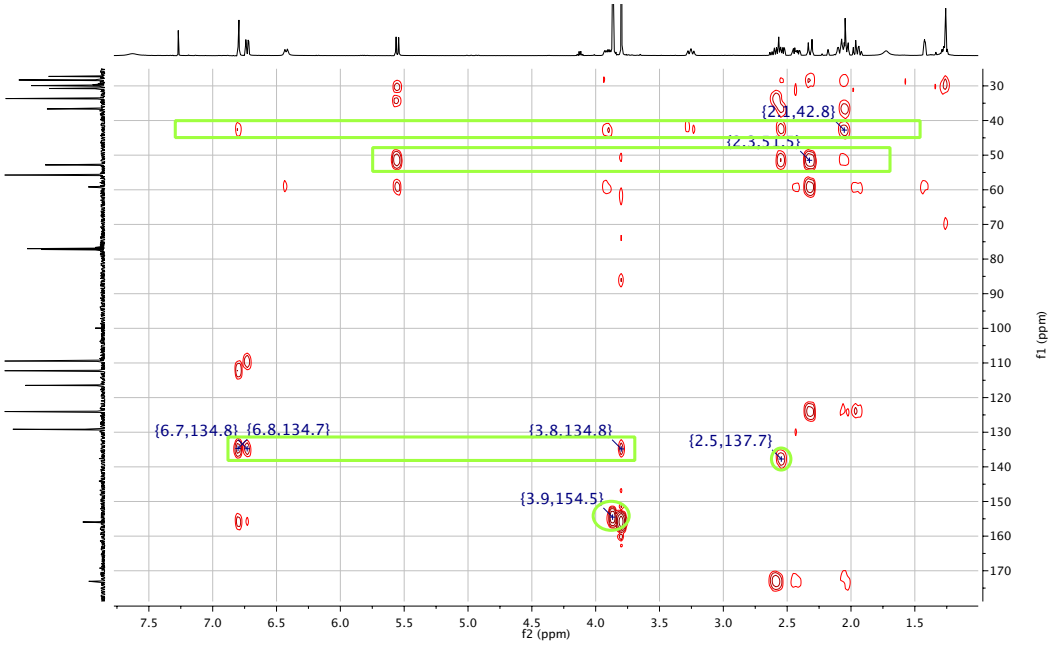


To a solution of (±)-(*Z*,*E*)-**96** (83 mg, 0.15 mmol, 1 equiv) in anhydrous CH_2Cl_2 (18 mL) in a sealed MW vial, was added $BF_3{\cdot}OEt_2$ (41 μL, 0.33 mmol, 2.2 equiv). The mixture was stirred vigorously and heated at 80 ºC for 2–3 h (full conversion monitored by TLC). The resulting red solution was allowed to cool to room temperature then filtered through a pad of basic alumina washing with acetone (3 × 40 mL). The volatiles were removed under vacuum and the crude mixture was purified by preparative silica gel TLC eluting with EtOAc to afford the title product as an off-white crystalline solid (43.5 mg, 0.119 mmol, yield = 79%).

M.p. 152-154 ºC (*Note:* at this temperature, the olefin migration might be effective and this melting point may represent a mixture of migrated and non-migrated cyclopropane compounds). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.65 (br s, 1H), 6.80 (d, *J* = 2.6 Hz, 1H), 6.73 (dd, *J* = 8.9, 2.6 Hz, 1H), 6.42 (d, *J* = 9.8 Hz, 1H), 5.55 (dd, *J* = 10.3, 1.3 Hz, 1H), 3.95 – 3.85 (m, 4H), 3.80 (s, 3H), 3.31 – 3.23 (m, 1H), 2.64 – 2.51 (m, 2H), 2.43 (ddd, *J* = 16.8, 9.0, 3.5 Hz, 1H), 2.32 (dt, *J* = 14.7, 1.6 Hz, 1H), 2.12 – 2.01 (m, 3H), 1.95 (dt, *J* = 12.6, 9.3 Hz, 1H), 1.42 (dd, *J* = 3.6, 1.4 Hz, 1H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 173.0, 155.9, *154.5*, *137.6*, *134.8*, 129.2, 124.1, 116.5, 112.2, 109.5, 59.2, 55.8, 52.8, *51.4*, *42.5*, 36.7, 33.7, 30.8, 29.9, 28.3, 27.3. *Note:* the signals between "*" were confirmed or could only be observed in the 2D ^{13}C-^{1}H correlation (HMQC, HMBC), see below. **HRMS** (ESI+) *m/z* calc. for $C_{21}H_{23}N_2O_4^+$ $[M+H]^+$: 367.1652, found: 367.1650.

The structure of this compound was unambiguously confirmed by single crystal X-ray crystallography analysis (see below for more details). Solvent system for crystallization: acetone, ethyl acetate.

HMBC correlation:

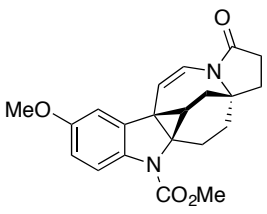


(–)-Methyl (5a*R*,5b*S*,6a*S*,12a*R*)-2-methoxy-9-oxo-5b,6,8,9,11,12-hexahydro-5*H*,7*H*-5a,6a-ethenopyrrolo[1'',2'':1',7']azepino[4',5':2,3]cyclopropa[1,2-*b*]indole-5-carboxylate ((–)-48)

To a solution of the hydrazone (+)-(*S*,*Z*,*E*)-**96** (55 mg, 0.1 mmol, 1 equiv) in anhydrous CH_2Cl_2 (12 mL) in a sealed MW vial, was added $BF_3{\cdot}OEt_2$ (27 µL, 0.22 mmol, 2.2 equiv). The mixture was stirred vigorously and heated at 80 ºC for 2–3 h (full conversion monitored by TLC). The mixture was then filtered through a pad of basic alumina washing with acetone (3 × 25 mL). The volatiles were removed under vacuum and the crude mixture was purified by preparative silica gel TLC eluting with EtOAc to afford the title product as a yellow gum (29.2 mg, 0.08 mmol, yield = 80%).

Analytical data identical to the ones of the racemic compound. $\boldsymbol{\alpha_D^{589}}$ ($CHCl_3$, *c* 1.02, 301 K) = – 105.8 deg.cm^2.g^{-1}.

(±)-Methyl (5a*R,5b*S**,6a*S**,12a*R**)-2-methoxy-9-oxo-5b,6,8,9,11,12-tetrahydro-5*H*,7*H*-5a,6a-ethanopyrrolo[1'',2'':1',7']azepino[4',5':2,3]cyclopropa[1,2-*b*]indole-5-carboxylate ((±)-97)**



In a dry MW vial (sealed), a solution of (±)-**48** (29.6 mg, 0.081 mmol, 1 equiv) in anhydrous toluene (2 mL) was heated at 155 ºC for 2 h (full conversion monitored by TLC). The volatiles were then removed *in vacuo* and the resulting mixture was

redissolved in the minimum amount of CH_2Cl_2 and purified by preparative silica gel TLC eluting with cyclohexane/EtOAc 1 : 2 to afford the title compound as yellow amorphous solid (28.4 mg, 0.078 mmol, yield = 96%).

M.p. 162-164 ºC. **^{1}H NMR** (500 MHz, $CDCl_3$, 328K) δ 7.52 (br d, *J* = 8.8 Hz, 1H), 6.92 (d, *J* = 2.5 Hz, 1H), 6.89 (d, *J* = 10.7 Hz, 1H), 6.71 (dt, *J* = 8.7, 2.1 Hz, 1H), 5.06 (d, *J* = 10.7 Hz, 1H), 3.91 (s, 3H), 3.82 (s, 3H), 2.78 (dd, *J* = 15.3, 5.7 Hz, 1H), 2.53 – 2.44 (m, 2H), 2.39 (dd, *J* = 17.2, 9.1 Hz, 1H), 2.29 (dd, *J* = 15.0, 6.0 Hz, 1H), 2.08 (ddd, *J* = 15.3, 12.9, 5.5 Hz, 1H), 1.89 (dd, *J* = 12.5, 8.5 Hz, 1H), 1.83 – 1.73 (m, 3H), 1.47 (d, *J* = 5.8 Hz, 1H). **^{13}C NMR** (126 MHz, $CDCl_3$, 328K) δ 172.2, 156.3, 154.7, 137.0, 135.7, 121.9, 116.3, 112.0, 109.4, 102.4, 61.5, 55.7, 52.7, 39.0, 35.3, 34.1, 32.9, 31.6, 29.6, 29.1, 21.8. **HRMS** (ESI+) *m/z* calc. for $C_{21}H_{22}N_2O_4Na^+$ $[M+Na]^+$: 389.1472, found: 389.1461.

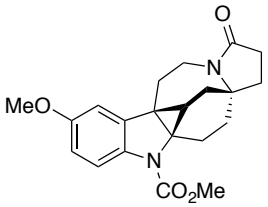
(–)-Methyl (5a*R*,5b*S*,6a*S*,12a*R*)-2-methoxy-9-oxo-5b,6,8,9,11,12-tetrahydro-5*H*,7*H*-5a,6a-ethanopyrrolo[1'',2'':1',7']azepino[4',5':2,3]cyclopropa[1,2-*b*]indole-5-carboxylate ((–)-97)

In a dry MW vial (sealed), a solution of (–)-**48** (29.2 mg, 0.08 mmol) in anhydrous toluene (2 mL) was heated at 155 ºC for 2 h (full conversion monitored by TLC). The volatiles were then removed *in vacuo* and the resulting mixture was redissolved in the minimum amount of CH_2Cl_2 and purified by preparative silica gel TLC eluting with cyclohexane/EtOAc 1 : 2 to afford the title compound as an off-white solid (27.7 mg, 0.076 mmol, yield = 95%).

Analytical data identical to the ones of the racemic compound. **M.p.** 224-226 ºC (>98% *ee*). $\boldsymbol{\alpha_D^{589}}$ ($CHCl_3$, *c* 0.85, 301 K) = – 112.9 deg.cm^2.g^{-1}.

The structure of this compound was unambiguously confirmed by single crystal X-ray crystallography analysis (see below for more details). Solvent system for crystallization: acetone, dichloromethane.

(±)-Methyl (5a*R,5b*S**,6a*S**,12a*R**)-2-methoxy-9-oxo-5b,6,8,9,11,12-hexahydro-5*H*,7*H*-5a,6a-ethanopyrrolo[1'',2'':1',7']azepino[4',5':2,3]cyclopropa[1,2-*b*]indole-5-carboxylate ((±)-105)**



Sodium cyanoborohydride (196 mg, 3.12 mmol, 5 equiv) was added by portion, though a solid addition dosing funnel, to a solution of (±)-**97** (230 mg, 0.63 mmol, 1 equiv) in a 2:1 mixture of formic acid / THF (7 mL) under argon at 25 ºC. The resulting mixture was stirred at 40 ºC for 2 h and a second portion of sodium cyanoborohydride (196 mg, 3.12 mmol, 5 equiv) was added and the mixture stirred for additional 2 h. A last addition of sodium cyanoborohydride (196 mg, 3.12 mmol, 5 equiv) was performed and the mixture heated at 40 ºC for additional 2 h, upon which time full conversion was observed by TLC (this operation may be repeated until full conversion is reached). The reaction was allowed to cool to room temperature and quenched by slow addition of a saturated aqueous solution of $NaHCO_3$. It was then diluted with EtOAc (80 mL) and brine (40 mL). The aqueous layer was re-extracted with EtOAc (3 × 80 mL) and the combined organic layers concentrated under reduced pressure. The crude mixture was redissolved in CH_2Cl_2 (200 mL) and washed with water (50 mL) and a saturated solution of $NaHCO_3$ (2 × 100 mL). The organic layer was dried over $MgSO_4$, filtered and purified by column chromatography on silica gel eluting with cyclohexane/EtOAc 1 : 2 to afford the title product as a colourless solid (206 mg, 0.56 mmol, yield = 89%).

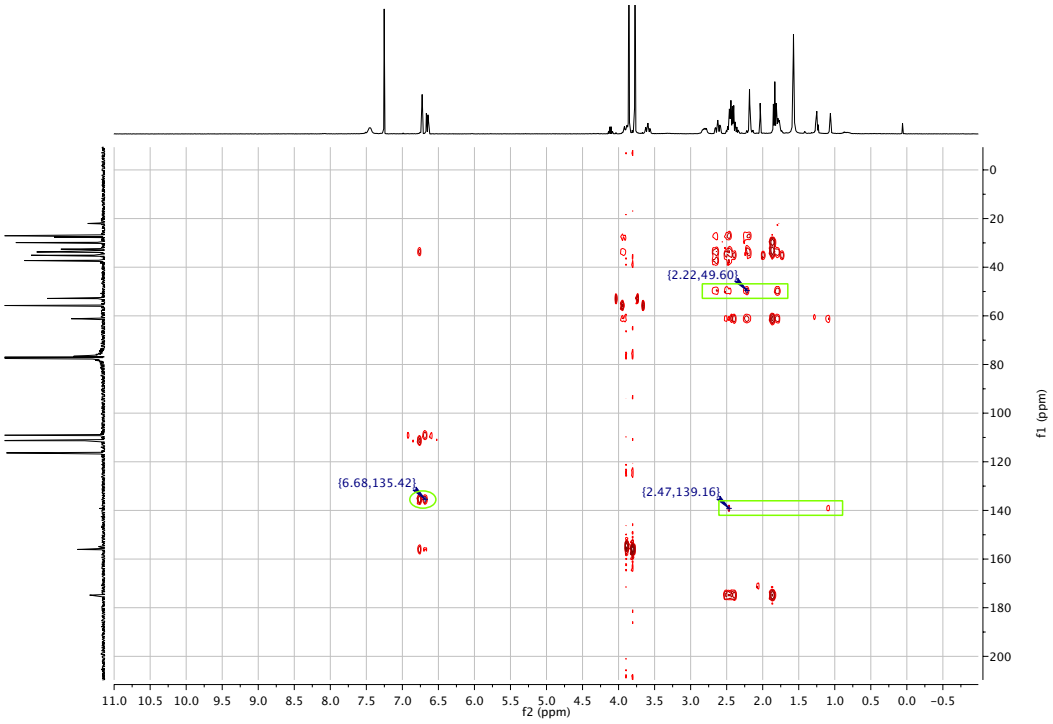
Caution! A large amount of HCN is generated upon addition of $NaCNBH_3$. The system should be connected to a trap filled with NaOH solution.

The structure of this compound was unambiguously confirmed by single crystal X-ray crystallography analysis (see below for more details). Solvent system for crystallization: ether, pentane, dichloromethane, and cyclohexane.

M.p. = 172-173 ºC. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.47 (br s, 1H), 6.75 (d, *J* = 2.6 Hz, 1H), 6.67 (dd, *J* = 8.8, 2.6 Hz, 1H), 3.96 – 3.85 (m, 4H), 3.79 (s, 3H), 3.61 (ddd, *J* = 14.4, 11.1, 3.2 Hz, 1H), 2.88 – 2.77 (m, 1H), 2.64 (ddd, *J* = 15.2, 10.8, 4.3 Hz, 1H), 2.53 – 2.35 (m, 4H), 2.25 – 2.16 (m, 2H), 1.90 – 1.74 (m, 4H), 1.08 (dd, *J* = 4.5, 2.1 Hz, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 174.8, 156.1, 154.9, *139.2*, *135.4*, 116.4, 111.3, 109.1, 61.2, 55.8, 52.9, *49.6*, 37.3, 35.1, 33.7, 33.7, 32.6, 29.9, 27.7, 27.1, 22.0. *Note:* the signals between "*" were only detected or confirmed by 2D ^{13}C-^{1}H

correlation (HMQC, HMBC), see below. **HRMS** (ESI+) *m/z* calc. for $C_{21}H_{25}N_2O_4^+$ $[M+H]^+$: 369.1809, found: 369.1806.

HMBC correlation:



(–)-Methyl (5a*R*,5b*S*,6a*S*,12a*R*)-2-methoxy-9-oxo-5b,6,8,9,11,12-hexahydro-5*H*,7*H*-5a,6a-ethanopyrrolo[1'',2'':1',7']azepino[4',5':2,3]cyclopropa[1,2-*b*]indole-5-carboxylate ((–)-105)

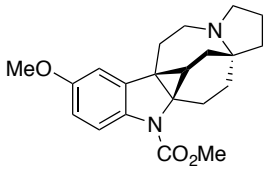
Sodium cyanoborohydride (28.3 mg, 0.45 mmol, 5 equiv) was added by portion, though a solid addition dosing funnel, to a solution of (–)-**97** (33 mg, 0.09 mmol, 1 equiv) in a 2:1 mixture of formic acid / THF (0.9 mL) under argon at 25 ºC. The resulting mixture was stirred at 40 ºC for 2 h and a second portion of sodium cyanoborohydride (28.3 mg, 0.45 mmol, 5 equiv) was added and the mixture stirred for additional 2 h (if complete conversion was not achieved, the same operation was repeated every 2 h until full conversion). Then the reaction was allowed to cool to room temperature and quenched by slow addition of saturated aqueous solution of $NaHCO_3$. It was then diluted with EtOAc (10 mL) and brine (5 mL). The aqueous layer was re-extracted with EtOAc (3 × 25 mL) and the combined organic layers concentrated under reduced pressure. The crude mixture was redissolved in CH_2Cl_2 (50 mL) and washed with water (20 mL) and a saturated solution of $NaHCO_3$ (2 × 50 mL). The organic layer was dried over $MgSO_4$,

filtered and purified by preparative silica gel TLC eluting with cyclohexane/EtOAc 1 : 2 to afford the title product as a colourless solid (30 mg, 0.081 mmol, yield = 90%).

Caution! A large amount of HCN is generated upon addition of $NaCNBH_3$. The system should be connected to a trap filled with NaOH solution.

Analytical data identical to the ones of the racemic compound. **M.p.** 187-190 ºC (>98% *ee*). $\boldsymbol{\alpha_D^{589}}$ ($CHCl_3$, *c* 1.50, 300 K) = – 70.7 deg.cm^2.g^{-1}.

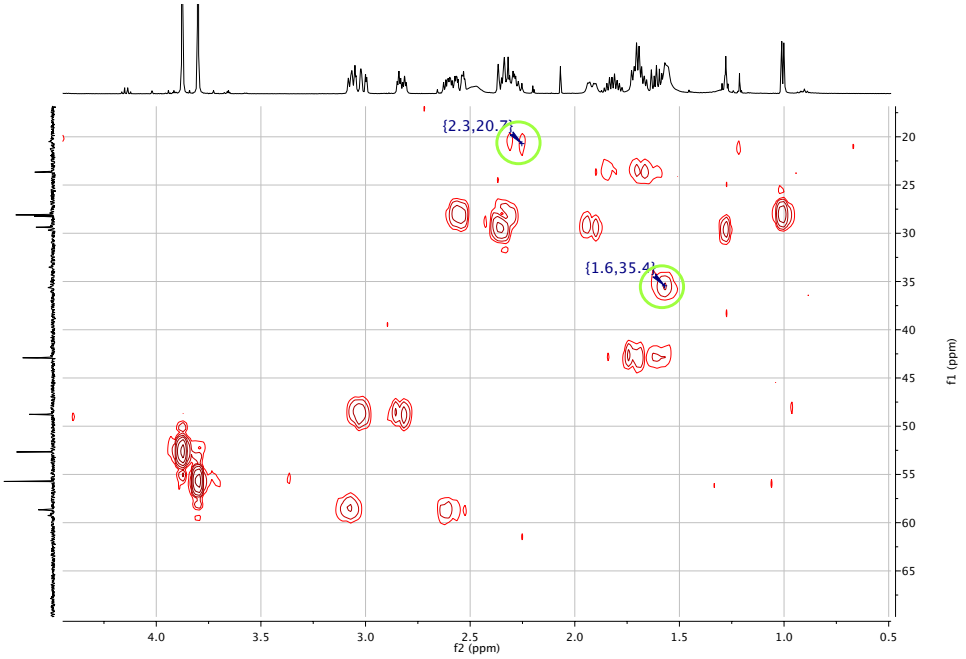
(±)-Lundurine C ((±)-3)



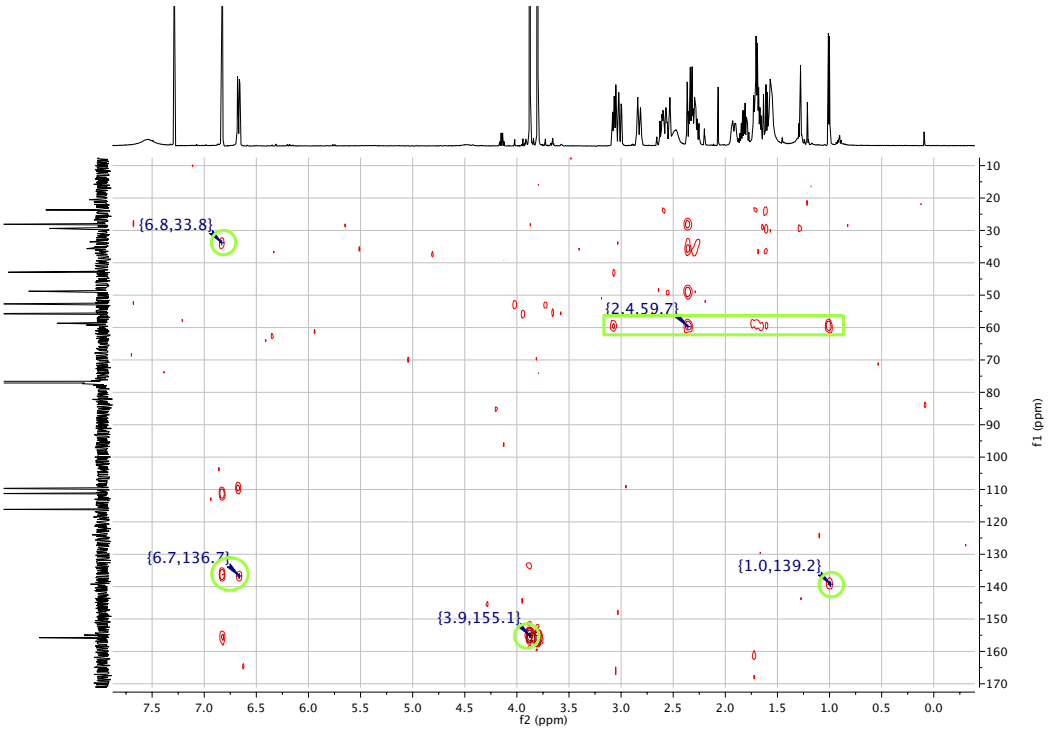
In a dry 10 mL flask under argon, a solution of $BH_3{\cdot}SMe_2$ (1M in CH_2Cl_2, 0.25 mL, 0.25 mmol, 10 equiv) was added to a solution of (±)-**105** (9.1 mg, 0.025 mmol, 1 equiv) in anhydrous THF (1 mL) at 25 ºC. The resulting colorless solution was stirred vigorously at 25 ºC for 3 h. The solution was cooled to 0 ºC and acetic acid (100 µL, 1.75 mmol, 70 equiv) was added and stirring was continued for 30 min at 25 ºC until effervescence had ceased. The reaction was quenched by addition of a saturated aqueous solution of $NaHCO_3$ (*ca.* 5 mL, caution: very vigorous effervescence) and basified until pH ≈ 10 by addition of solid $NaHCO_3$. It was then diluted with EtOAc (8 mL) and the aqueous layer was re-extracted with EtOAc (3 × 8 mL). The combined organic extracts were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by preparative neutral alumina TLC eluting with cyclohexane/EtOAc 1 : 1 to afford (±)-lundurine C as a pale yellow oil (7 mg, 0.02 mmol, yield = 80%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.52 (br s, 1H), 6.81 (d, *J* = 2.6 Hz, 1H), 6.65 (dd, *J* = 8.8, 2.6 Hz, 1H), 3.86 (s, 3H), 3.79 (s, 3H), 3.09 – 2.97 (m, 2H), 2.82 (dt, *J* = 13.4, 4.2 Hz, 1H), 2.65 – 2.43 (m, 3H), 2.37 – 2.23 (m, 3H), 1.91 (dd, *J* = 14.5, 5.4 Hz, 1H), 1.80 (qq, *J* = 10.3, 5.3, 4.0 Hz, 1H), 1.73 – 1.49 (m, 5H), 0.99 (d, *J* = 5.0 Hz, 1H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 155.8, *154.9*, *139.1*, *136.2*, 116.1, 111.3, 109.7, *59.7*, 58.7, 55.7, 52.7, 48.8 (2C), 42.9, *35.3*, *33.5*, 29.4, 28.1, 28.1, 23.6, *20.5*. *Note:* the signals between "*" were confirmed by 2D ^{13}C-^{1}H correlation (HMQC, HMBC), see below. **HRMS** (ESI+) *m/z* calc. for $C_{21}H_{27}N_2O_3^+$ $[M+H]^+$: 355.2016, found: 355.2010.

HMQC correlation:



HMBC correlation:



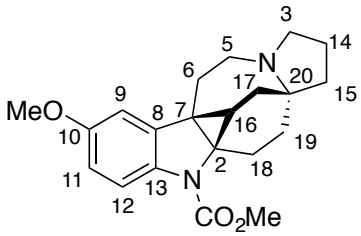
(–)-Lundurine C ((–)-3)

In a dry 10 mL flask under argon, a solution of $BH_3{\cdot}SMe_2$ (1M in CH_2Cl_2, 0.37 mL, 0.37 mmol, 10 equiv) was added to a solution of (–)-**105** (13.7 mg, 0.037 mmol, 1 equiv) in anhydrous THF (1 mL) at 25 ºC. The resulting colourless solution was stirred vigorously at 25 ºC for 3 h. The solution was cooled to 0 ºC and acetic acid (148 µL, 2.6 mmol, 70 equiv) was added and stirring was continued for 30 min at 25 ºC until effervescence had ceased. The reaction was quenched by addition of a saturated aqueous solution of $NaHCO_3$ (*ca.* 5 mL, caution: very vigorous effervescence) and basified until pH ≈ 10 by addition of solid $NaHCO_3$. It was then diluted with EtOAc (10 mL) and the aqueous layer was re-extracted with EtOAc (3 × 10 mL). The combined organic extracts were dried over Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was purified by preparative neutral alumina TLC eluting with cyclohexane/EtOAc 1 : 1 to afford (–)-lundurine C as a pale yellow oil (11.1 mg, 0.031 mmol, yield = 84%).

Analytical data identical to the one of the racemic compound. **HPLC** (Chiralpak IA (250 mm × 4.6 mm), hexane/ethanol/ethylenediamine 94.8 : 5 : 0.2, 1 mL/min) t_R (*major*) 8.3 min, t_R (*minor*) 9.8 – 9.9 min, >98% *ee*. $\boldsymbol{\alpha_D^{589}}$ ($CHCl_3$, *c* 0.98, 300 K) = – 1.1 ± 0.6 deg.cm^2.g^{-1}; $\boldsymbol{\alpha_D^{589}}$ (CH_2Cl_2, *c* 0.3, 301 K) = – 6.2 ± 0.8 deg.cm^2.g^{-1}. *Note:* the error on measurement of the optical rotation is given in this case, because of the low value observed.

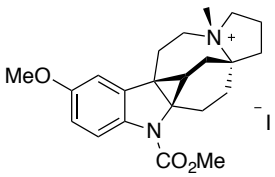
The HPLC analysis of this sample confirms its enantiopurity (> 98% *ee*) and the X-ray crystal structure of its *N*-Me ammonium salt confirms the (5a*R*,5b*S*,6a*R*,12a*R*) absolute configuration as reported for lundurines A–C (see crystal data below).

Table 12: Comparison with NMR data of isolated lundurine C



Position	^{13}C NMR of isolated lundurine C (d ppm)[9,10]	^{13}C NMR of our synthetic lundurine C (d ppm)
N<u>C</u>O$_2$Me	154.9	154.9 (0)
NCO$_2$<u>Me</u>	52.7	52.7 (0)
2	48.7	48.8 (+0.1)
3	58.6	58.7 (+0.1)
5	48.7	48.8 (+0.1)
6	27.9	28.1 (+0.2)
7	33.4	33.5 (+0.1)
8	138.9	139.1 (+0.2)
9	109.6	109.7 (+0.1)
10	155.7	155.8 (+0.1)
OMe	55.7	55.7 (0)
11	111.3	111.3 (0)
12	116.1	116.1 (0)
13	136.1	136.2 (+0.1)
14	23.5	23.6 (+0.1)
15	42.7	42.9 (+0.2)
16	27.9	28.1 (+0.2)
17	29.3	29.4 (+0.1)
18	20.3	20.5 (+0.2)
19	35.1	35.3 (+0.2)
20	60.0	59.6 (–0.4)

(–)-Lundurine C *N*-Me ammonium iodide salt (106)



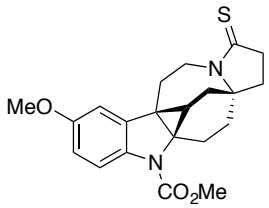
Lundurine C (–)-**3** (6.9 mg, 0.019 mmol, 1 equiv) was dissolved in iodomethane (200 µL) at 25 ºC and the mixture stirred vigorously at 25 ºC. A yellow solid started precipitating and stirring was continued until full conversion of starting material was observed by TLC (*ca.* 3 h). The volatiles were removed under reduced pressure to afford the title product as a yellow solid (8.9 mg, 0.018 mmol, yield = 92%). Obtained as a *ca.* 2 : 1 mixture of diastereoisomers at nitrogen. Crystallization from acetone / CH_2Cl_2 / cyclohexane allowed us to obtain a single crystal suitable for single crystal X-

ray diffraction (see below for more details). Solvent system for crystallization: acetone, dichloromethane, and cyclohexane.

M.p. >190 ºC decomposition. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.43 (br, 1H *major* + 1H *minor*), 6.89 (d, *J* = 2.6 Hz, 1H *minor*), 6.81 (d, *J* = 2.6 Hz, 1H *major*), 6.69 (dd, *J* = 8.9, 2.6 Hz, 1H *major* + 1H *minor*), 4.40 – 4.30 (m, 1H *major* + 1H *minor*), 4.28 – 4.17 (m, 1H *major* + 1H *minor*), 4.05 – 3.94 (m, 1H *major* + 1H *minor*), 3.87 (s, 3H *minor*), 3.85 (s, 3H *major*), 3.79 (s, 3H *minor*), 3.79 (s, 3H *major*), 3.43 (s, 3H *major*), 3.36 (s, 3H *minor*), 3.25 – 1.83 (m, 13H *major* + 13H *minor*), 1.16 (dd, *J* = 4.0, 1.8 Hz, 1H *minor*), 1.13 (dd, *J* = 4.0, 1.8 Hz, 1H *major*). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 156.2, 156.2, 154.7, 152.4, 137.3, 135.1, 116.8, 116.7, 113.1, 112.7, 109.5, 108.7, 77.7, 77.2, 70.8, 65.7, 62.6, 60.4, 55.9, 55.9, 53.4, 53.1, 53.0, 48.0, 46.5, 45.5, 41.5, 38.1, 33.1, 32.1, 30.4, 29.0, 28.1, 26.4, 25.9, 24.2, 21.9, 21.6, 20.8, 18.0. **HRMS** (ESI+) *m/z* calc. for $C_{22}H_{29}N_2O_3^+$ $[M–I^-]^+$: 369.2173, found: 369.2167.

4. Total synthesis of lundurines A and B

(±)-Methyl (5a*R,5b*S**,6a*S**,12a*R**)-2-methoxy-9-thioxo-5b,6,8,9,11,12-hexahydro-5*H*,7*H*-5a,6a-ethanopyrrolo[1'',2'':1',7']azepino[4',5':2,3]cyclopropa[1,2-*b*]indole-5-carboxylate ((±)-111)**



A solution of (±)-**105** (28.2 mg, 0.077 mmol, 1 equiv) and Lawesson's reagent (31 mg, 0.077 mmol, 1 equiv) in dry toluene (0.75 mL) in a sealed microwave vial was stirred at 90 ºC until full conversion of starting material was achieved (typically 1 h). The volatiles were removed under reduced pressure and the resulting crude product was redissolved in the minimum amount of CH_2Cl_2 and purified by preparative silica gel TLC eluting with CH_2Cl_2/acetone 40 : 1 to afford the title compound as an amorphous off-white solid (28.7 mg, 0.075 mmol, yield = 98%). *Note:* the compound was crystallized from CH_2Cl_2/Et_2O/pentane to measure the melting point.

M.p. (CH_2Cl_2/Et_2O/pentane) = 158-160 ºC. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.46 (br d, *J* = 8.8 Hz, 1H), 6.74 (d, *J* = 2.6 Hz, 1H), 6.68 (dd, *J* = 8.8, 2.6 Hz, 1H), 4.74 (dt, *J* = 15.0, 4.8 Hz, 1H), 3.91 – 3.82 (m, 4H), 3.79 (s, 3H), 3.08 – 3.01 (m, 2H), 2.93 (dd, *J* = 15.6, 8.9 Hz, 1H), 2.77 (ddd, *J* = 15.2, 11.9, 4.3 Hz, 1H), 2.58 – 2.49 (m, 2H), 2.31 (dt, *J* = 14.8, 1.8 Hz, 1H), 2.24 (dd, *J* = 14.9, 5.1 Hz, 1H), 1.98 – 1.82 (m, 4H), 1.11 (dd, *J* = 5.1, 1.4 Hz, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 201.6, 156.1, 154.8, 138.9, 135.3,

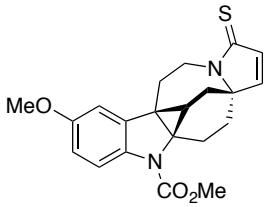
116.5, 111.5, 108.9, 69.3, 55.7, 52.9, 49.6, 42.5, 42.4, 36.8, 33.4, 32.7, 31.3, 26.8, 26.6, 21.6. **HRMS** (ESI+) *m/z* calc. for $C_{21}H_{24}N_2O_3SNa^+$ $[M+Na]^+$: 407.1400, found: 407.1391.

(–)-Methyl (5a*R*,5b*S*,6a*S*,12a*R*)-2-methoxy-9-thioxo-5b,6,8,9,11,12-hexahydro-5*H*,7*H*-5a,6a-ethanopyrrolo[1'',2'':1',7']azepino[4',5':2,3]cyclopropa[1,2-*b*]indole-5-carboxylate ((–)-111)

A solution of (–)-**105** (29.1 mg, 0.079 mmol, 1 equiv) and Lawesson's reagent (32 mg, 0.079 mmol, 1 equiv) in dry toluene (0.8 mL) in a sealed microwave vial was stirred at 90 ºC until full conversion of starting material was achieved (1 h). The volatiles were removed under reduced pressure and the resulting crude product was redissolved in the minimum amount of CH_2Cl_2 and purified by preparative silica gel TLC eluting with CH_2Cl_2/acetone 40 : 1 to afford the title compound as an off-white amorphous solid (29.1 mg, 0.076 mmol, yield = 96%). <u>*Note:*</u> the compound was precipitated from CH_2Cl_2/Et_2O/pentane to measure the melting point.

Analytical data identical to the ones of the racemic compound. **M.p.** (CH_2Cl_2/Et_2O/pentane) = 167-169 °C. $\boldsymbol{\alpha_D^{589}}$ ($CHCl_3$, *c* 1.05, 298 K) = – 127.5 deg.cm^2.g^{-1}.

(±)-Methyl (5a*R,5b*S**,6a*R**,12a*R**)-2-methoxy-9-thioxo-5b,6,11,12-tetrahydro-5*H*,9*H*-5a,6a-ethanopyrrolo[1'',2'':1',7']azepino[4',5':2,3]cyclopropa[1,2-*b*]indole-5-carboxylate ((±)-112)**



A solution of (±)-**111** (51.1 mg, 0.133 mmol, 1 equiv) in dry CH_2Cl_2 (2.7 mL) was placed in a sealed microwave vial and cooled at –20 ºC. *N*,*N*-Diisopropylethylamine (Hünig's base, 280 µL, 1.61 mmol, 12 equiv) and *para*-toluenesulfinyl chloride[56] (140.3 mg, 0.8 mmol, 6 equiv) were subsequently added. The reaction mixture was stirred at –20 ºC until full conversion of starting material was observed by TLC (1 h). The mixture was then heated at 80 ºC and stirred for additional 4 h. The brown solution was allowed to cool to 25 ºC, the volatiles were removed under vacuum and the crude mixture was purified by preparative silica gel TLC eluting with CH_2Cl_2/acetone 40 : 1 to afford the title product as a yellow foamy solid (38.4 mg, 0.10 mmol, yield = 75%). <u>*Note:*</u> the compound was crystallized from CH_2Cl_2/Et_2O/pentane to measure the melting point.

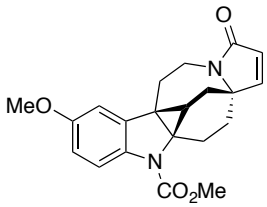
M.p. (CH_2Cl_2/Et_2O/pentane) = 195-197 ºC. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.47 (br d, *J* = 8.8 Hz, 1H), 6.83 (d, *J* = 5.5 Hz, 1H), 6.73 (d, *J* = 2.5 Hz, 1H), 6.69 (dd, *J* = 8.7, 2.6 Hz, 1H), 6.43 (d, *J* = 5.5 Hz, 1H), 5.21 (dt, *J* = 15.5, 4.2 Hz, 1H), 3.89 (s, 3H), 3.80 (s, 3H), 3.70 (ddd, *J* = 15.7, 12.5, 3.7 Hz, 1H), 2.97 (dd, *J* = 15.5, 9.2 Hz, 1H), 2.84 – 2.66 (m, 3H), 2.52 (dd, *J* = 14.9, 5.7 Hz, 1H), 2.18 (td, *J* = 13.1, 9.3 Hz, 1H), 1.96 (ddd, *J* = 14.9, 2.2, 1.0 Hz, 1H), 1.66 (ddd, *J* = 14.2, 7.1, 2.0 Hz, 1H), 1.16 (d, *J* = 4.9 Hz, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 194.3, 156.2, 154.8, 154.1, 139.0, 135.0, 133.7, 116.5, 111.4, 108.8, 74.6, 55.8, 53.0, 49.9, 41.0, 33.3, 29.2, 27.6, 27.1, 25.7, 19.7. **HRMS** (ESI+) *m/z* calc. for $C_{21}H_{23}N_2O_3S^+$ $[M+H]^+$: 383.1424, found: 383.1419.

(–)-Methyl (5a*R*,5b*S*,6a*R*,12a*R*)-2-methoxy-9-thioxo-5b,6,11,12-tetrahydro-5*H*,9*H*-5a,6a-ethanopyrrolo[1'',2'':1',7']azepino[4',5':2,3]cyclopropa[1,2-*b*]indole-5-carboxylate ((–)-112)

A solution of (–)-**111** (29 mg, 0.076 mmol, 1 equiv) in dry CH_2Cl_2 (1.5 mL) was placed in a sealed microwave vial and cooled at –20 ºC. *N*,*N*-Diisopropylethylamine (Hünig's base, 158 μL, 0.91 mmol, 12 equiv) and *para*-toluenesulfinyl chloride[55]**Error! Bookmark not defined.** (79.6 mg, 0.456 mmol, 6 equiv) were subsequently added. The reaction mixture was stirred at –20 ºC until full conversion of starting material was observed by TLC (1 h). The mixture was then heated at 80 ºC and stirred for additional 4 h. The brown solution was allowed to cool to 25 ºC, the volatiles were removed under vacuum and the crude mixture was purified by preparative silica gel TLC eluting with CH_2Cl_2/acetone 40 : 1 to afford the title product as a yellow amorphous solid (19.5 mg, 0.051 mmol, yield = 68%).

Analytical data identical to the ones of the racemic compound. **M.p.** = 131-133 ºC. **α_D^{589}** ($CHCl_3$, *c* 0.975, 296 K) = – 202.1 deg.cm^2.g^{-1}.

(±)-Lundurine A ((±)-1)



A solution of (±)-**112** (7.6 mg, 0.02 mmol, 1 equiv) in anhydrous CH_2Cl_2 (0.5 mL) was placed in a dry Schlenk tube under argon. The solution was cooled to –78 ºC and a freshly prepared solution of *m*-CPBA (*ca.* 75% purity, 100 mg in 5 mL anhydrous CH_2Cl_2, 0.51 mL, 0.044 mmol, 2.2 equiv) was added dropwise at –78 ºC. The solution was stirred at this temperature for 30 min, upon which time, full conversion of the starting material was observed by TLC. The mixture was filtered through a short pad of

basic alumina (5 cm high, 1.5 cm diameter), first flushing with CH_2Cl_2 (30 mL) then CH_2Cl_2/acetone (4 : 1, 100 mL). The fractions containing the product were concentrated in *vacuo* to afford analytically pure lundurine A (5.1 mg, 0.014 mmol, yield = 70%). *Note:* the compound was crystallized from CH_2Cl_2/Et_2O/pentane to measure the melting point.

M.p. (CH_2Cl_2/Et_2O/pentane) = 172-174 ºC. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.46 (br s, 1H), 6.88 (d, *J* = 5.8 Hz, 1H), 6.73 (d, *J* = 2.6 Hz, 1H), 6.68 (dd, *J* = 8.8, 2.6 Hz, 1H), 6.10 (d, *J* = 5.8 Hz, 1H), 4.31 (dt, *J* = 15.0, 4.3 Hz, 1H), 3.88 (s, 3H), 3.80 (s, 3H), 3.53 (ddd, *J* = 14.7, 12.3, 3.6 Hz, 1H), 2.91 (dd, *J* = 14.5, 9.7 Hz, 1H), 2.74 (ddd, *J* = 15.5, 12.6, 7.0 Hz, 1H), 2.70 – 2.59 (m, 2H), 2.47 (dd, *J* = 14.6, 5.7 Hz, 1H), 2.12 (td, *J* = 13.0, 9.0 Hz, 1H), 1.85 (dd, *J* = 14.7, 1.3 Hz, 1H), 1.58 (dddd, *J* = 13.6, 6.8, 2.5, 1.0 Hz, 1H), 1.13 (d, *J* = 5.0 Hz, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 169.8, 156.1, 154.8, 154.1, 139.4, 135.1, 125.1, 116.4, 111.2, 108.9, 65.6, 55.8, 52.9, 50.0, 36.1, 33.7, 30.6, 28.9, 27.9, 26.1, 20.5. **HRMS** (ESI+) *m/z* calc. for $C_{21}H_{23}N_2O_4^+$ $[M+H]^+$: 367.1652, found: 367.1651.

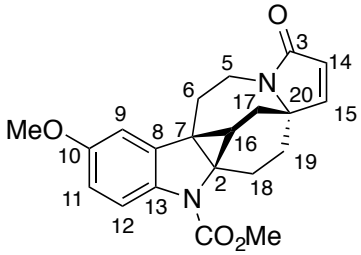
(–)-Lundurine A ((–)-1)

A solution of (–)-**112** (18.8 mg, 0.049 mmol, 1 equiv) in anhydrous CH_2Cl_2 (1 mL) was placed in a dry Schlenk tube under argon. The solution was cooled to –78 ºC and a freshly prepared solution of *m*-CPBA (*ca.* 75% purity, 100 mg in 5 mL anhydrous CH_2Cl_2, 1 mL, 0.087 mmol, 1.77 equiv) was added dropwise at –78 ºC. The solution was stirred at this temperature for 30 min, upon which time, full conversion of the starting material was observed by TLC. The mixture was filtered through a short pad of basic alumina (5 cm high, 1.5 cm diameter), first flushing with CH_2Cl_2 (30 mL) then CH_2Cl_2/acetone (4 : 1, 100 mL). The fractions containing the product were concentrated in *vacuo* to afford analytically pure lundurine A (12.5 mg, 0.034 mmol, yield = 69%) as a colorless crystalline solid.

Note: the compound was crystallized from acetone/Et_2O/cyclohexane to measure the melting point. The structure of this compound was unambiguously confirmed by single crystal X-ray crystallography analysis (see below for more details). Solvent system for crystallization: acetone, cyclohexane.

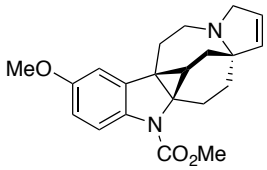
Analytical data identical to the ones of the racemic compound. **M.p.** (acetone/Et_2O/cyclohexane) = 207-208 ºC. **HPLC** (Chiralpak IA (250 mm × 4.6 mm), hexane/dichloromethane/ethanol 69 : 30 : 1, 1 mL/min) t_R (*minor*) 13.6–13.9 min, t_R (*major*) 16.5–16.6 min, 98% *ee*. $\boldsymbol{\alpha_D^{589}}$ ($CHCl_3$, *c* 0.625, 298 K) = – 121.2 deg.cm^2.g^{-1}.

Table 13: Comparison with NMR data of isolated and previously synthesized lundurine A



Position	^{13}C NMR of isolated lundurine A (d ppm)[9,10]	^{13}C NMR of synthetic lundurine A (d ppm) (Group of Qin)[15]	^{13}C NMR of our synthetic lundurine A (d ppm)
N<u>C</u>O$_2$Me	154.8	154.8	154.8 (0)
NCO$_2$<u>Me</u>	52.9	52.9	52.9 (0)
2	50.1	50.0	50.0 (–0.1)
3	169.8	169.8	169.8 (0)
5	36.1	36.1	36.1 (0)
6	27.9	27.9	27.9 (0)
7	33.6	33.6	33.7 (+0.1)
8	139.4	139.4	139.4 (0)
9	108.9	108.9	108.9 (0)
10	156.1	156.1	156.1 (0)
OMe	55.7	55.8	55.8 (+0.1)
11	111.2	111.2	111.2 (0)
12	116.3	116.4	116.4 (+0.1)
13	135.0	135.1	135.1 (+0.1)
14	125.1	125.1	125.1 (0)
15	154.1	154.1	154.1 (0)
16	26.0	26.0	26.1 (+0.1)
17	30.6	30.6	30.6 (0)
18	20.5	20.5	20.5 (0)
19	28.9	28.9	28.9 (0)
20	65.6	65.6	65.6 (0)

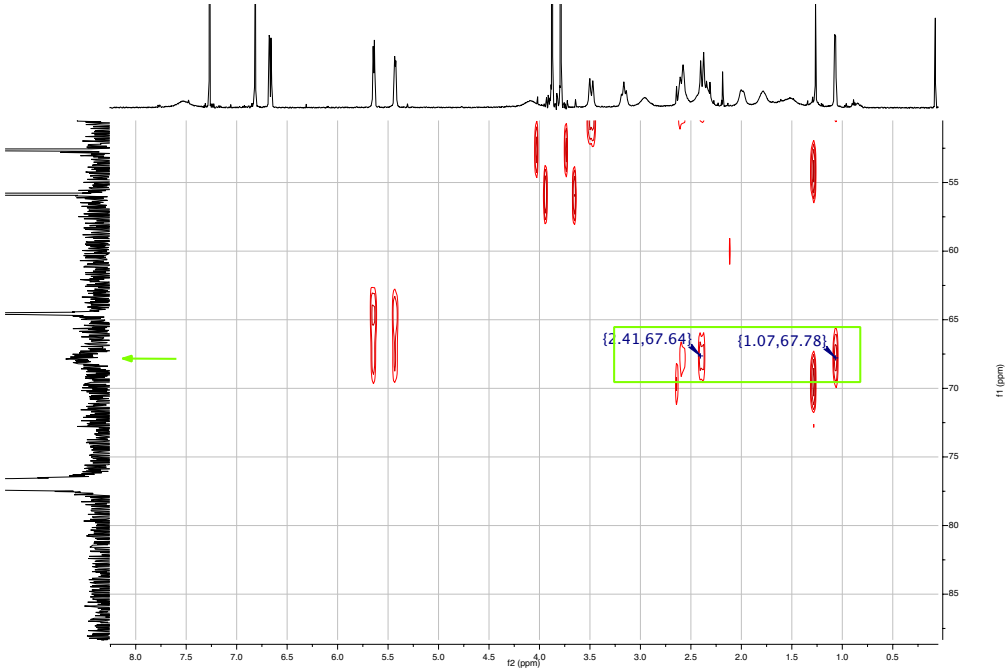
(±)-Lundurine B ((±)-2)



In a sealed vial under argon, a solution of (±)-**112** (9.2 mg, 0.024 mmol, 1 equiv) in iodomethane (240 µL) was heated at 50 ºC for 2 h. The excess iodomethane was concentrated under reduced pressure and the resulting crude mixture dissolved in methanol (0.5 mL), cooled at 0 ºC and treated with $NaBH_4$ (5.5 mg, 0.145 mmol, 6 equiv), added in two portions. The mixture was stirred at 0 ºC for 30 min and allowed to warm to 25 ºC. The volatiles were removed under vacuum and the excess reagent quenched by addition of brine (5 mL). The aqueous layer was basified, if necessary, to pH ≈ 10, with 1M aqueous NaOH. The crude product was extracted with CH_2Cl_2 (4 × 10 mL), the combined organic extracts dried over Na_2SO_4, filtered and concentrated *in vacuo*. Purification by preparative neutral aluminium oxide TLC eluting with EtOAc/cyclohexane 1 : 1 afforded lundurine B as a pale brown oil (6.4 mg, 0.018 mmol, yield = 76%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.52 (br s, 1H), 6.82 (d, *J* = 2.7 Hz, 1H), 6.67 (dd, *J* = 8.8, 2.7 Hz, 1H), 5.64 (d, *J* = 6.0 Hz, 1H), 5.43 (d, *J* = 6.1 Hz, 1H), 4.09 (br s, 1H), 3.87 (s, 3H), 3.79 (s, 3H), 3.49 (d, *J* = 14.9, 1H), 3.16 (t, *J* = 12.5 Hz, 1H), 2.96 (br s, 1H), 2.64 – 2.52 (m, 2H), 2.50 – 2.28 (m, 3H), 2.05 – 1.92 (m, 1H), 1.79 (br s, 1H), 1.52 (br s, 1H), 1.07 (d, *J* = 5.2 Hz, 1H). **^{13}C NMR** (126 MHz, $CDCl_3$, 328K) δ 156.1, 154.9, 139.0, 137.6, 136.4, 124.5, 116.4, 111.7, 109.9, *67.8*, 64.6, 55.8, 52.6, 50.3, 48.3, 34.3, 33.6, 28.6, 28.3, 27.9, 20.0. *Note:* the signal between "*" was confirmed by 2D ^{13}C-^{1}H correlation (HMBC), see below. **HRMS** (ESI+) *m/z* calc. for $C_{21}H_{25}N_2O_3^+$ $[M+H]^+$: 353.1860, found: 353.1866.

HMBC correlation:

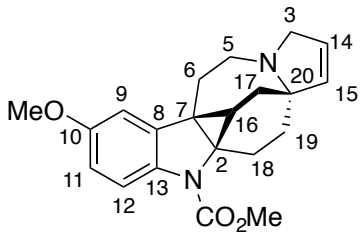


(–)-Lundurine B ((–)-2)

In a sealed vial under argon, a solution of (–)-**112** (17.6 mg, 0.046 mmol, 1 equiv) in iodomethane (300 µL) was heated at 50 ºC for 2 h. The excess iodomethane was concentrated under reduced pressure and the resulting crude mixture dissolved in methanol (1 mL), cooled at 0 ºC and treated with $NaBH_4$ (10.1 mg, 0.267 mmol, *ca.* 6 equiv). The mixture was stirred at 0 ºC for 30 min and allowed to warm to 25 ºC and stirred for additional 2 h. The volatiles were removed under vacuum, the excess reagent quenched by addition of brine (5 mL) and the aqueous layer basified, if necessary, to pH ≈ 10 with 1M aqueous NaOH. The crude product was extracted with CH_2Cl_2 (4 × 10 mL), the combined organic extracts dried over Na_2SO_4, filtered and concentrated *in vacuo*. Purification by preparative neutral aluminium oxide TLC eluting with EtOAc/cyclohexane 1 : 1 afforded lundurine B as a pale brown oil (11.6 mg, 0.033 mmol, yield = 72%).

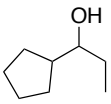
Analytical data identical to the racemic sample. **HPLC** (Chiralpak IA (250 mm × 4.6 mm), hexane/(isopropanol-ethylenediamine 0.2%) 95 : 5, 0.9 mL/min) t_R(*minor*) 12.4 min, t_R (*major*) 13.9–14.2 min, 98% *ee*. $\boldsymbol{\alpha_D^{589}}$ ($CHCl_3$, *c* 0.5025, 301 K) = – 19.4 deg.cm^2.g^{-1}.

Lundurine B



Position	^{13}C NMR of isolated lundurine B (d ppm)[9,10]	^{13}C NMR of synthetic lundurine B (d ppm) (Group of Nishida)[14]	^{13}C NMR of our synthetic lundurine B (d ppm)
N<u>C</u>O$_2$Me	154.9	154.9	154.9 (0)
NCO$_2$<u>Me</u>	52.7	52.7	52.6 (–0.1)
2	48.1	48.0	48.3 (+0.2)
3	64.6	64.6	64.6 (0)
5	50.2	50.2	50.3 (+0.1)
6	28.5	28.5	28.6 (+0.1)
7	33.4	33.5	33.6 (+0.2)
8	139.0	139.1	139.0 (0)
9	109.7	109.8	109.9 (+0.2)
10	155.8	155.8	156.1 (+0.3)
OMe	55.7	55.8	55.8 (+0.1)
11	111.3	111.4	111.7 (+0.4)
12	116.2	116.2	116.4 (+0.2)
13	136.2	136.2	136.4 (+0.2)
14	124.6	124.6	124.5 (–0.1)
15	137.6	137.6	137.6 (0)
16	28.2	28.2	28.3 (+0.1)
17	27.6	27.6	27.9 (+0.3)
18	19.8	19.9	20.0 (+0.2)
19	34.5	34.5	34.3 (–0.2)
20	67.6	67.6	67.8 (+0.2)

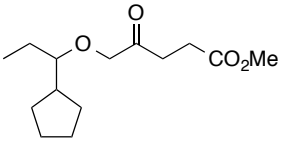
5. Mechanistic studies on ene-lactam intermediates 77k



(±)-1-Cyclopentylpropan-1-ol ((±)-**79k**) was prepared according to the same procedure used for the preparation of (±)-**79f** using ethylmagnesium bromide 3M in THF.[57]

^{1}H NMR (500 MHz, $CDCl_3$) δ 3.33 (td, *J* = 7.8, 3.4 Hz, 1H), 1.88 (ddt, *J* = 16.5, 8.9, 7.7 Hz, 1H), 1.82 – 1.74 (m, 1H), 1.72 – 1.49 (m, 6H), 1.46 – 1.29 (m, 3H), 1.25 – 1.15 (m, 1H), 0.96 (t, J = 7.4 Hz, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 77.3, 45.9, 29.1, 28.8, 28.5, 25.7, 25.6, 10.0. **MS** (EI+) *m/z* 127.1 ($[M - H]^+$, <5%), 99.1 ($[M - Et]^+$, 70%), 81.1 $[C_6H_9]^+$, 100%), 59.1 [M – *c*-$C_5H_{11}]^+$, 70%). Data in agreement with the literature.[60]

(±) Methyl 5-(1-cyclopentylpropoxy)-4-oxopentanoate ((±)-74k)



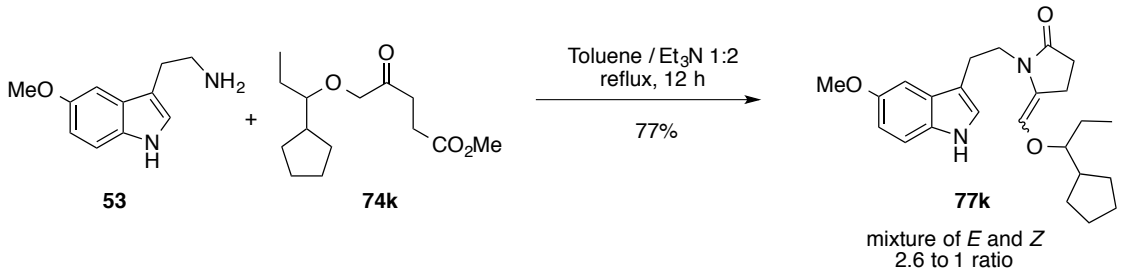
Indium (III) triflate (29 mg, 0.051 mmol, 2 mol %) was dissolved in alcohol (±)-**74k** (1.64 g, 12.8 mmol, 5 equiv) in an oven-dried Schlenk tube under Ar atmosphere and the solution was cooled at 0 ºC. Methyl 5-diazo-4-oxopentanoate **81** (400 mg, 2.56 mmol, 1 equiv) was slowly added via syringe pump (over 15 min) at 0 ºC. The resulting mixture was allowed to warm slowly to 25 ºC (over 1 h) and stirred for 2 further h at 25 ºC. The resulting mixture was loaded on a short pad of silica gel washed with pentane/Et_2O 4:1. The fraction containing the mixture of alcohol and oxoester were collected and concentrated. The resulting viscous liquid was redissolved in dichloromethane (20 mL) and triethylamine (2.1 mL, 25.6 mmol, 10 equiv) was added followed by addition of a few crystals of DMAP and Ac_2O (1.8 mL, 19.2 mmol, 7.5 equiv) dropwise at 25 ºC. The mixture was stirred at 25 ºC for one h and the volatiles were removed *in vacuo*. The resulting oil was loaded on silica gel column and purified by chromatography eluting with pentane/Et_2O 95 : 5 to 2 : 1 to afford the title product as a pale yellow oil (165 mg, 0.64 mmol, yield = 25%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 4.12 (d, *J* = 16.6 Hz, 1H), 4.01 (d, *J* = 16.6 Hz, 1H), 3.69 (s, 3H), 3.14 (dt, *J* = 7.5, 5.3 Hz, 1H), 2.88 (t, *J* = 6.6 Hz, 2H), 2.62 (t, *J* = 6.6 Hz, 2H), 2.06 (ddt, *J* = 16.9, 9.3, 7.6 Hz, 1H), 1.86 – 1.77 (m, 1H), 1.71 – 1.47 (m, 7H), 1.43 – 1.33 (m, 1H), 1.27 – 1.16 (m, 1H), 0.92 (t, *J* = 7.4 Hz, 3H). **^{13}C NMR** (126 MHz,

(60) Fernández-Mateos, E.; Maciá, B.; Yus, M., *Adv. Synth. Catal.* **2013**, *355*, 1249–1254.

$CDCl_3$) δ 208.4, 173.2, 85.8, 74.8, 51.8, 43.0, 34.0, 29.2, 29.1, 27.2, 25.5, 25.5, 24.4, 9.0. **HRMS** (ESI+) *m/z* calc. for $C_{14}H_{24}O_4Na^+$ $[M+Na]^+$: 279.1567, found: 279.1565.

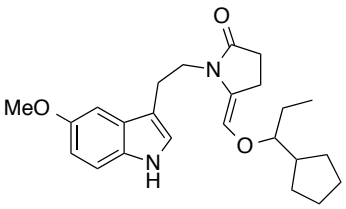
(±)-(*E/Z*)-5-((1-cyclopentylpropoxy)methylene)-1-(2-(5-methoxy-1*H*-indol-3-yl)ethyl)pyrrolidin-2-one ((±)-77k)



In a dry 25 mL round-bottom flask, 5-methoxytryptamine (95 mg, 0.5 mmol, 1 equiv) was suspended in triethylamine (8 mL) and (±)-**74k** (128 mg, 0.5 mmol, 1 equiv) was added as a solution in toluene (4 mL). The flask was equipped with a Dean-Stark apparatus and the mixture heated at 130 ºC (reflux) for 12 h, then cooled to room temperature and the solvents evaporated.

The crude mixture was redissolved in CD_2Cl_2 and the ^{1}H NMR indicated a 2.6:1 ratio of *E*/*Z* isomers. The crude mixture was purified by silica gel preparative TLC eluting with dichloromethane/acetone 93:7 to afford the mixture of ene-lactams as a pale brown oil (152 mg, 0.383 mmol, combined yield = 77%). The two isomers could be partially separated and the pure fraction of each isomer was used in the equilibration experiments (see below).

(±)-(*E*)-5-((1-cyclopentylpropoxy)methylene)-1-(2-(5-methoxy-1*H*-indol-3-yl)ethyl)pyrrolidin-2-one ((±)-(*E*)-77k)

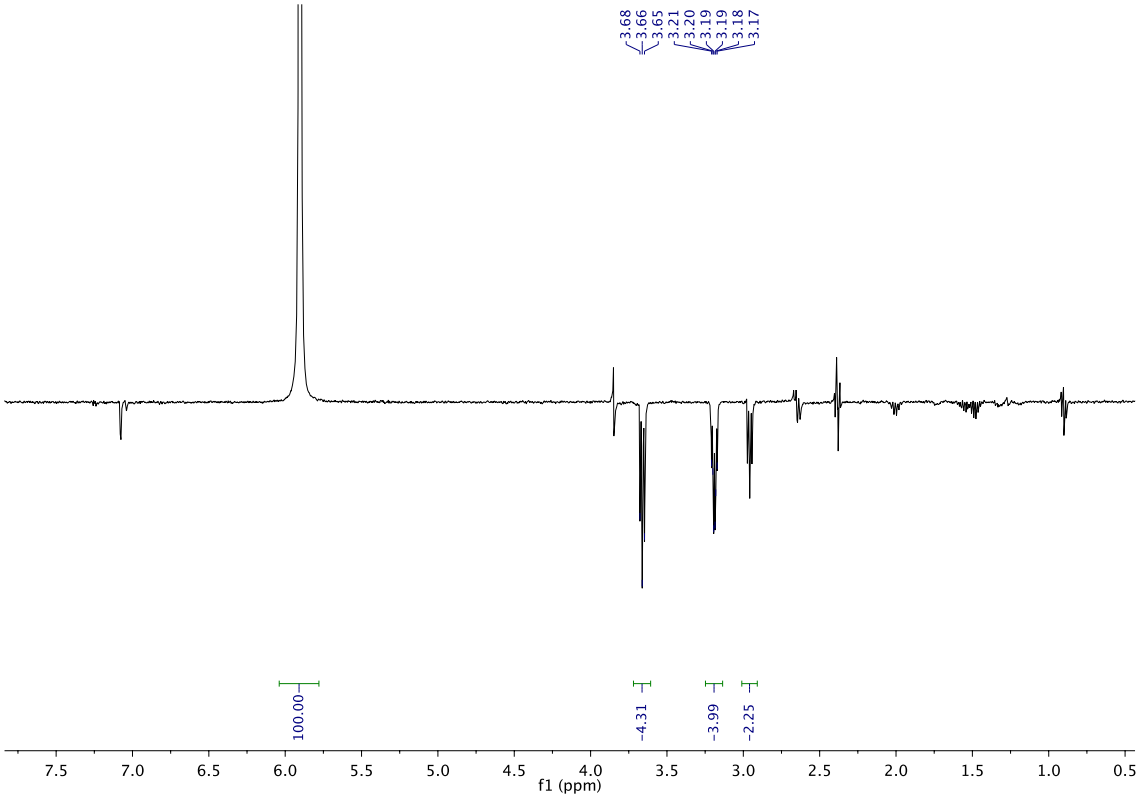


^{1}H NMR (500 MHz, CD_2Cl_2) δ 8.13 (br s, 1H), 7.25 (dd, *J* = 8.8, 0.6 Hz, 1H), 7.08 (d, *J* = 2.4 Hz, 1H), 7.04 (d, *J* = 2.4 Hz, 1H), 6.82 (dd, *J* = 8.8, 2.4 Hz, 1H), 5.90 (t, *J* = 2.2 Hz, 1H, C=C***H***), 3.85 (s, 3H), 3.66 (dd, *J* = 8.3, 6.6 Hz, 2H, N-C***H₂***), 3.19 (td, *J* = 7.0, 4.4 Hz, 1H, O-C***H***), 2.96 (dd, *J* = 8.0, 7.0 Hz, 2H, N-CH_2C***H₂***), 2.67 – 2.62 (m, 2H), 2.41 – 2.38 (m, 2H), 2.01 (ddt, *J* = 16.8, 9.1, 7.7 Hz, 1H), 1.78 – 1.70 (m, 1H), 1.69 – 1.43 (m, 7H), 1.37 – 1.29 (m, 1H), 1.25 – 1.16 (m, 1H), 0.90 (t, *J* = 7.4 Hz, 3H). **^{13}C NMR** (126 MHz, CD_2Cl_2) δ 174.6, 154.5, 131.8, 128.4, 126.5, 125.5, 123.2, 113.1, 112.4, 112.3, 100.7,

87.9, 56.1, 43.8, 41.2, 29.5, 29.4, 29.3, 26.1, 26.0, 25.9, 22.9, 20.2, 9.6. **HRMS** (ESI+) *m/z* calc. for $C_{24}H_{32}N_2O_3Na^+$ $[M+Na]^+$: 419.2305, found: 419.2294.

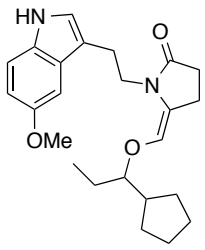
The *E*-olefin geometry was confirmed by nOe experiments (see below).

nOe experiment: irradiation at 5.90 ppm



The olefin C***H*** is correlated to both C***H₂*** of the tryptamine residue, confirming the *E*-configuration.

(±)-(*Z*)-5-((1-cyclopentylpropoxy)methylene)-1-(2-(5-methoxy-1*H*-indol-3-yl)ethyl)pyrrolidin-2-one ((±)-(*Z*)-77k)

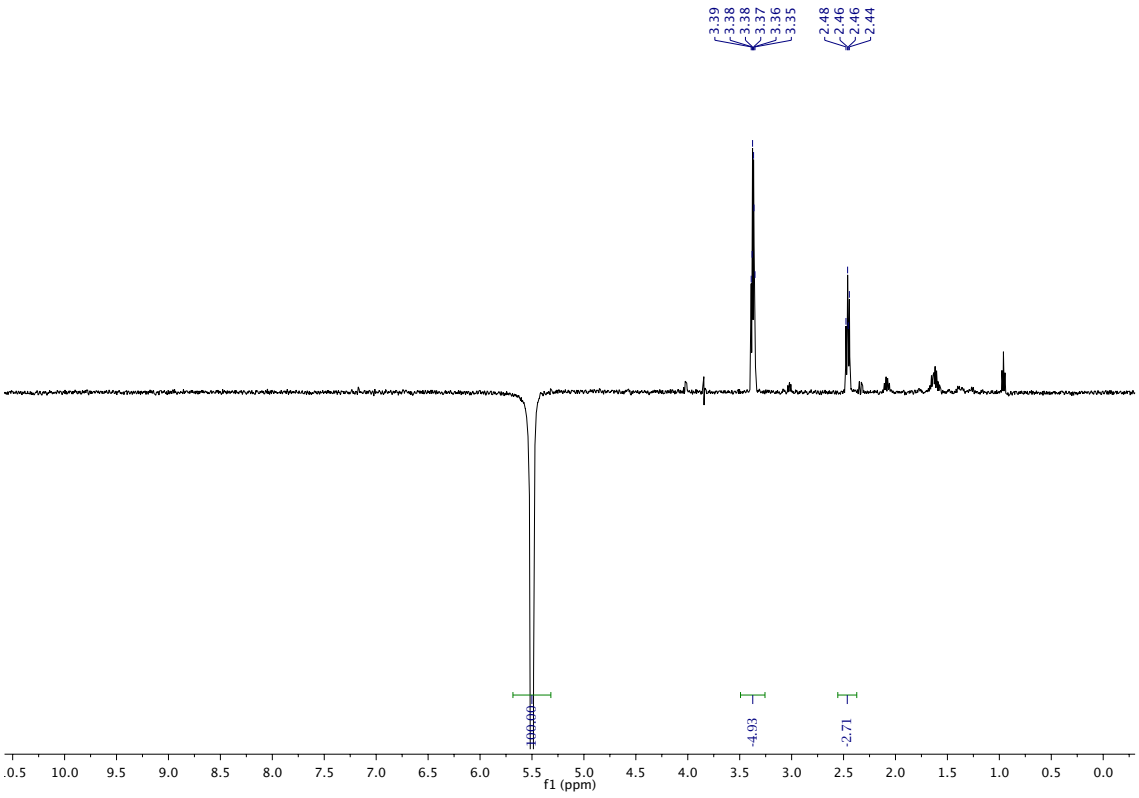


^{1}H NMR (500 MHz, CD_2Cl_2) δ 7.99 (br s, 1H), 7.23 (d, *J* = 7.4 Hz, 1H), 7.17 (d, *J* = 2.4 Hz, 1H), 7.01 (d, *J* = 2.4 Hz, 1H), 6.80 (dd, *J* = 8.8, 2.5 Hz, 1H), 5.50 (t, *J* = 1.6 Hz, 1H, C=C***H***), 4.02 (t, *J* = 7.7 Hz, 2H, N-C***H₂***), 3.84 (s, 3H), 3.37 (td, *J* = 6.7, 4.7 Hz, 1H, O-C***H***), 3.04 – 2.99 (m, 2H, N-CH_2C***H₂***), 2.48 – 2.43 (m, 2H, C=C-C***H₂***), 2.35 – 2.30 (m, 2H, C***H₂***-C=O), 2.08 (ddt, *J* = 15.0, 9.2, 7.7 Hz, 1H), 1.81 – 1.73 (m, 1H), 1.71 – 1.45 (m, 7H), 1.43 – 1.34 (m, 1H), 1.32 – 1.23 (m, 1H), 0.96 (t, *J* = 7.4 Hz, 3H). **^{13}C NMR** (126 MHz, CD_2Cl_2) δ 175.3, 154.3, 131.7, 128.7, 124.8, 122.8, 118.0, 113.7, 112.3, 112.0, 101.2, 88.7, 56.1, 44.1, 42.7, 30.2, 29.5, 29.1, 26.7, 25.9, 25.9, 25.2, 21.8,

10.0. **HRMS** (ESI+) *m/z* calc. for $C_{24}H_{32}N_2O_3Na^+$ $[M+Na]^+$: 419.2305, found: 419.2306.

The *Z*-olefin geometry was confirmed by nOe experiments (see below).

nOe experiment: irradiation at 5.50 ppm

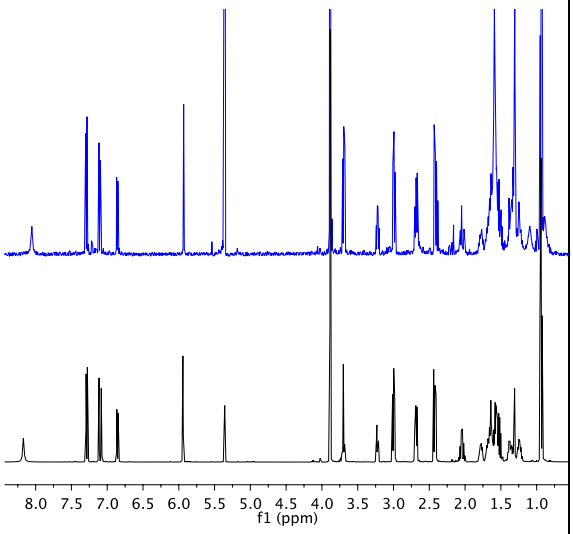


The olefin C***H*** is correlated to the C***H₂*** *a* to the enamine C=C bond, confirming the *Z*-configuration.

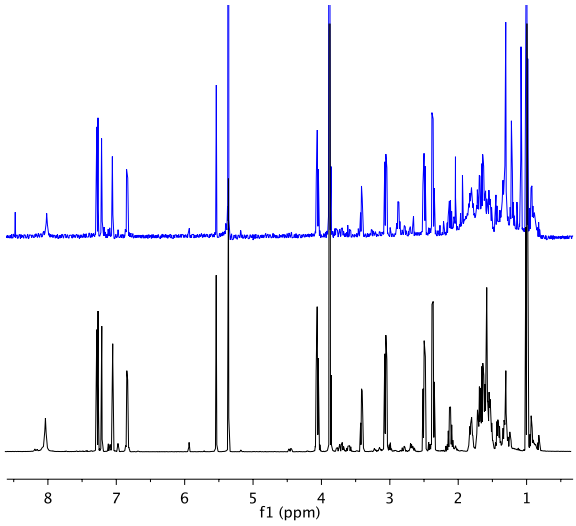
Equilibration experiments:

Both *E*-**77k** and *Z*-**77k** (5 mg each) were separately heated at 100 ºC in 0.5 mL of a stock solution of [toluene (3.3 mL), Et_3N (6.6 mL), MeOH (10 µL) and water (10 µL)], in a sealed vial. After 16 h, the solvent was removed and the residue analyzed by ^1H NMR. The ^1H NMR unambiguously showed that neither of the isomers had undergone equilibration (see below).

Equilibration of *E*-isomer (t = 0 in black; t = 16 h in blue)



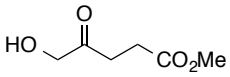
Equilibration of *Z*-isomer (t = 0 in black; t = 16 h in blue)



Details on unsuccessful approaches:

1. Initial strategy for formation of tetrasubstituted C20

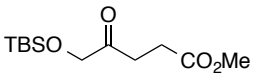
Methyl 5-hydroxy-4-oxopentanoate (58)



Methyl 5-hydroxy-4-oxopentanoate (**58)** was prepared according to the literature.[25]

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.32 (d, *J* = 4.8 Hz, 2H), 3.69 (s, 3H), 3.02 (t, *J* = 4.9 Hz, 1H), 2.71 (s, 4H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 208.0, 172.7, 68.2, 52.0, 32.8, 27.5. NMR data were in accordance with previously reported.[25]

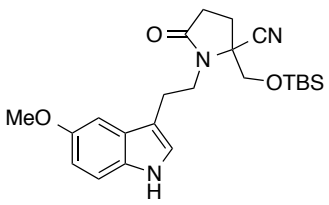
Methyl 5-((*tert*-butyldimethylsilyl)oxy)-4-oxopentanoate (54)



DBU (3.95 mL, 26.4 mmol, 1.1 equiv.) and TBSCl (4.33 g, 28.8 mmol, 1.2 equiv.) were added to a solution of the alcohol **58** (3.51 g, 24 mmol, 1.1 equiv.) in dry CH_2Cl_2 (48 mL) at 0 °C under argon atmosphere. The reaction was stirred for 15 h at 25 °C. the mixture was quenched with brine (50 mL) and aqueous phase was extracted with CH_2Cl_2 (2 × 30 mL). The combined organic layers were washed with brine, dried over Na_2SO_4 and purified by column chromatography (cyclohexane/EtOAc 10 : 1) to give the oxoester (5.58 mL, 21.8 mmol, 91%) as a colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.21 (s, 2H), 3.67 (s, 3H), 2.83 (t, *J* = 6.6 Hz, 2H), 2.61 (t, *J* = 6.6 Hz, 2H), 0.93 (s, 9H), 0.09 (s, 6H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 209.4, 173.1, 69.2, 51.8, 33.2, 27.2, 25.7 (3C), 18.2, 5.6, 5.6. **HRMS** (ESI+) *m/z* calc. for $C_{12}H_{24}O_4SiNa^+$ $[M+Na]^+$: 283.1336, found: 283.1340

2-(((*tert*-butyldimethylsilyl)oxy)methyl)-1-(2-(5-methoxy-1*H*-indol-3-yl)ethyl)-5-oxopyrrolidine-2-carbonitrile (59)

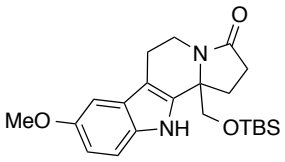


5-Methoxytryptamine (190 mg, 1 mmol, 1 equiv) was added to a stirring solution of methyl 5-((*tert*-butyldimethylsilyl)oxy)-4-oxopentanoate **54** (266 mg, 1.05 mmol, 1.05 equiv) in MeOH (2 mL) at 50 ºC under argon atmosphere. After 10 mins TMSCN (138 μL, 1.1 mmol, 1.1 equiv) followed by AcOH (1.15 mL, 20 mmol, 20 equiv) were added. The resulting solution was stirred for 5 h, quenched with sat. aqueous $NaHCO_3$ and aqueous phase was extracted with CH_2Cl_2 (2

× 30 mL). The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The title product was obtained after flash chromatography (cyclohexane/EtOAc 4 : 1 to EtOAc) as a brownish gum (273 mg, 0.65 mmol, yield = 64%) as well as the product of Pictet-Spengler type reaction **60** (120 mg, 0.30 mmol, yield = 30%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 (br s, 1H), 7.26 (d, *J* = 8.7, Hz, 1H), 7.23 (d, *J* = 2.4 Hz, 1H), 7.05 (d, *J* = 2.4 Hz, 1H), 6.87 (ddd, *J* = 8.8, 2.5, 0.5 Hz, 1H), 3.89 (s, 3H), 3.76 – 3.54 (m, 4H), 3.15 (ddd, *J* = 9.4, 6.9, 1.0 Hz, 2H), 2.59 – 2.42 (m, 3H), 2.29 (ddd, *J* = 12.3, 8.8, 6.2 Hz, 1H), 0.88 (s, 9H), 0.07 (s, 3H), 0.05 (s, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 174.5, 154.2, 131.3, 127.8, 122.7, 119.0, 112.7, 112.5, 111.9, 100.4, 66.0, 62.4, 55.9, 42.7, 28.9, 28.0, 25.6 (3C), 24.0, 18.1, -5.6, -5.7. **HRMS** (ESI+) *m/z* calc. for $C_{23}H_{34}N_3O_3Si^+$ $[M+H]^+$: 428.2364, found: 428.2372.

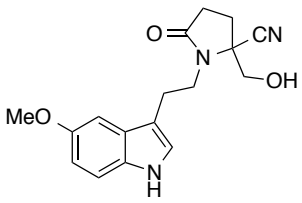
11b-((*tert*-butyldimethylsilyl)oxy)-8-methoxy-1,2,5,6,11,11b-hexahydro-3*H*-indolizino[8,7-*b*]indol-3-one (60)



White solid, 30%.

M.p. >143 ºC decomposition **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.46 (br s, 1H), 7.23 (d, *J* = 8.7, Hz, 1H), 6.97 (d, *J* = 2.4 Hz, 1H), 6.86 (dd, *J* = 8.8, 2.4 Hz, 1H), 4.52 (dd, *J* = 13.2, 5.2 Hz, 1H), 3.88 (s, 3H), 3.84 (d, *J* = 2.5 Hz, 2H), 3.11 (dddd, *J* = 12.9, 11.3, 5.2, 1.3 Hz, 1H), 2.86 (ddd, *J* = 15.2, 11.3, 6.0 Hz, 1H), 2.79 (ddd, *J* = 15.4, 5.3, 1.3 Hz, 1H), 2.78 – 2.60 (m, 2H), 2.44 (ddd, *J* = 16.2, 10.3, 1.4 Hz, 1H), 2.09 (dt, *J* = 12.1, 10.3 Hz, 1H), 0.94 (s, 9H), 0.08 (s, 3H), 0.06 (s, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 173.8, 154.2, 136.1, 131.2, 126.9, 112.1, 11.7, 107.5, 100.5, 66.7, 63.1, 55.9, 35.6, 31.0, 28.6, 25.8 (3C), 21.3, 18.2, -5.6 (2C). **HRMS** (ESI+) *m/z* calc. for $C_{22}H_{32}N_2O_3Na^+$ $[M+Na]^+$: 423.2074, found: 423.2080.

2-(hydroxymethyl)-1-(2-(5-methoxy-1*H*-indol-3-yl)ethyl)-5-oxopyrrolidine-2-carbonitrile (55)



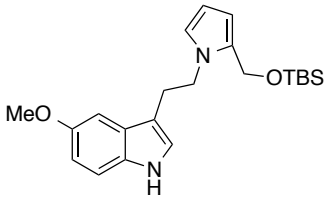
1M TBAF solution in THF (0.6 mL, 0.6 mmol, 1.2 equiv.) was added to a solution of the protected alcohol **59** (213 mg, 0.5 mmol, 1 equiv.) in dry THF (1 mL) at 25 °C. The reaction was stirred for 2 h at 25 °C then mixture quenched with brine (5 mL) and aqueous phase was extracted with CH_2Cl_2 (3 × 15 mL). The combined

organic layers were washed with brine, dried over Na_2SO_4 and purified by column chromatography (cyclohexane/EtOAc 1 : 1 to EtOAc) to give the free alcohol (151.8 mg, 0.48 mmol, 97%) as a white solid.

The structure of this compound was unambiguously confirmed by single crystal X-ray crystallography analysis (see below for more details). Solvent system for crystallization: dichloromethane, pentane.

M.p. 116 – 117.5 ºC. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 8.07 (br s, 1H), 7.23 (d, *J* = 8.7, Hz, 1H), 7.17 (d, *J* = 2.3 Hz, 1H), 6.96 (d, *J* = 2.5 Hz, 1H), 6.87 (ddd, *J* = 8.8, 2.4 Hz, 1H), 3.89 (s, 3H), 3.70 – 3.51 (m, 4H), 3.27 – 2.91 (m, 3H), 2.49 (dd, *J* = 8.6, 6.2 Hz, 2H), 2.42 – 2.26 (m, 2H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 174.5, 154.1, 131.3, 127.5, 123.0, 118.7, 112.6, 112.1, 112.1, 100.5, 65.0, 62.5, 56.0, 42.9, 29.1, 27.2, 23.7. **HRMS** (ESI+) *m/z* calc. for $C_{17}H_{20}N_3O_3Na^+$ $[M+H]^+$: 314.1499, found: 314.1502.

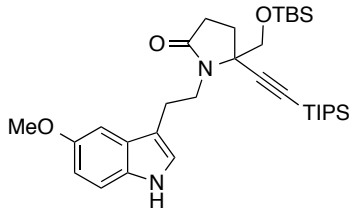
3-(2-(2-(((*tert*-butyldimethylsilyl)oxy)methyl)-1*H*-pyrrol-1-yl)ethyl)-5-methoxy-1*H*-indole (63)



1M DIBAL−H solution in toluene (0.4 mL, 0.4 mmol, 2 equiv.) was added to a solution of the nitrile **59** (85.4 mg, 0.2 mmol, 1 equiv.) in dry THF (1 mL) at −20 °C. The reaction was stirred for 1 h at 25 °C then mixture quenched with potassium sodium tartrate (5 mL) and aqueous phase was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were washed with brine, dried over Na_2SO_4 and purified by column chromatography (cyclohexane/EtOAc 4 : 1 to 1 : 1) to give the product (59.1 mg, 0.15 mmol, 77%) as a colourless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86 (br s, 1H), 7.25 (d, *J* = 8.7, Hz, 1H), 6.97 (d, *J* = 2.4 Hz, 1H), 6.87 (ddd, *J* = 8.8, 2.4 Hz, 1H), 6.85 (d, *J* = 2.3 Hz, 1H), 6.59 (t, *J* = 2.3 Hz, 1H), 6.04 – 6.01 (m, 2H), 4.57 (s, 2H), 4.35 – 4.15 (m, 2H), 3.87 (s, 3H), 3.21 (ddd, *J* = 8.2, 6.7, 0.8 Hz, 2H), 0.88 (s, 9H), 0.03 (s, 6H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 154.1, 131.5, 131.3, 127.7, 122.8, 121.8, 112.8, 112.3, 111.8, 108.3, 106.5, 100.5, 57.4, 55.9, 47.4, 27.8, 25.9 (3C), 18.3, -5.3 (2C). **HRMS** (ESI+) *m/z* calc. for $C_{22}H_{32}N_2O_2SiNa^+$ $[M+Na]^+$: 407.2125, found: 407.2136.

5-(((*tert*-butyldimethylsilyl)oxy)methyl)-1-(2-(5-methoxy-1*H*-indol-3-yl)ethyl)-5-((triisopropylsilyl)ethynyl)pyrrolidin-2-one (69)

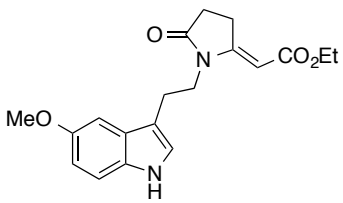


5-Methoxytryptamine (190 mg, 1 mmol, 1 equiv), methyl 5-((*tert*-butyldimethylsilyl)oxy)-4-oxopentanoate **54** (266 mg, 1.05 mmol, 1.05 equiv), CuCl (99 mg, 1 mmol, 1.0 equiv), (triisopropylsilyl)acetylene (447 µL, 2 mmol, 2 equiv) and Cs_2CO_3 (58 mg, 0.25 mmol, 0.25 equiv) were placed in a MW sealed vial under argon atmosphere. The vial was kept in ultrasound bath until system became indiscrete. The resulting mixture was heated neat at 110 ºC for 16 h, then allowed to cool to room temperature. The title product was obtained after flash chromatography (cyclohexane/EtOAc 3 : 1 to EtOAc) as a viscous brown oil (198 mg, 0.34 mmol, yield = 34%) as well as the product of Pictet-Spengler type reaction **60** (178 mg, 0.44 mmol, yield = 44%).

Note 1: the reaction is poorly reproducible; yield of desired product **69** for 1 mmol scale varieties from 17 to 40%.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.95 (br s, 1H), 7.27 (d, *J* = 2.2 Hz, 1H), 7.24 (d, *J* = 8.8 Hz, 1H), 7.00 (d, *J* = 2.1 Hz, 1H), 6.86 (dd, *J* = 8.7, 2.4 Hz, 1H), 3.89 (s, 3H), 3.87 (d, *J* = 10.4 Hz, 1H), 3.72 −3.60 (m, 2H), 3.52 (ddd, *J* = 13.6, 11.5, 5.2 Hz, 1H), 3.19 (ddd, *J* = 14.1, 11.7, 5.1 Hz, 1H), 3.06 (ddd, *J* = 14.0, 11.7, 5.2 Hz, 1H), 2.56 – 2.42 (m, 2H), 2.34 (ddd, *J* = 12.6, 9.4, 5.2 Hz, 1H), 2.27 (ddd, *J* = 12.6, 9.7, 8.0 Hz, 1H), 1.07 (s, 21H), 0.88 (s, 9H), 0.07 (s, 3H), 0.05 (s, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 175.2, 154.0, 131.3, 128.0, 122.1, 113.6, 112.5, 111.7, 106.7, 100.8, 86.7, 67.3, 62.9, 55.9, 41.4, 30.8, 30.1, 25.7 (3C), 24.6, 18.6 (6C), 18.1, 11.1 (3C), -5.5, -5.61. **HRMS** (ESI+) *m/z* calc. for $C_{33}H_{54}N_2O_3Na^+$ $[M+Na]^+$: 605.3565, found: 605.3560

Ethyl(*E*)-2-(1-(2-(5-methoxy-1*H*-indol-3-yl)ethyl)-5-oxopyrrolidin-2-ylidene)acetate (72)



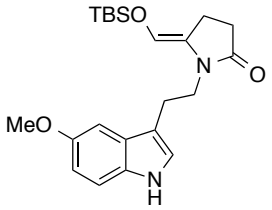
5-Methoxytryptamine (38 mg, 0.2 mmol, 1 equiv), diester ketone **71**[35] (55 mg, 0.21 mmol, 1.05 equiv), CuCl (9.9 mg, 1 mmol, 1.0 equiv) and (triisopropylsilyl)acetylene (44.7 µg, 2 mmol, 2 equiv) were placed in a MW sealed vial under argon atmosphere. The vial was kept in ultrasound bath until system became

indiscrete. The resulting mixture was heated at 95 ºC (reflux) for 16 h, then allowed to cool to room temperature. The title product was obtained after flash chromatography (cyclohexane/EtOAc 3 : 1 to 1 : 1) as a yellow solid (27 mg, 0.158 mmol, yield = 79%).

The structure of this compound was unambiguously confirmed by single crystal X-ray crystallography analysis (see below for more details). Solvent system for crystallization: chloroform, pentane.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08 (br s, 1H), 7.25 (d, *J* = 8.8 Hz, 1H), 7.13 (d, *J* = 2.4 Hz, 1H), 7.05 (d, *J* = 2.4, 1H), 6.87 (dd, *J* = 8.8, 2.4 Hz, 1H), 5.39 (d, *J* = 1.9 Hz, 1H), 4.19 (q, *J* = 7.2, 2H), 3.90 (s, 3H), 3.85 – 3.77 (m, 2H), 3.29 – 3.21 (m, 2H), 3.03 – 2.96 (m, 2H), 2.55 – 2.48 (m, 2H), 1.31 (t, *J* = 7.1 Hz, 3H).

(*E*)-5-(((*tert*-butyldimethylsilyl)oxy)methylene)-1-(2-(5-methoxy-1*H*-indol-3-yl)ethyl)pyrrolidin-2-one (73)



5-Methoxytryptamine (19 mg, 0.1 mmol, 1 equiv), methyl 5-((*tert*-butyldimethylsilyl)oxy)-4-oxopentanoate **54** (27 mg, 0.1 mmol, 1.05 equiv), CuCl (9.9 mg, 1.1 mmol, 1.0 equiv) and (triisopropylsilyl)acetylene (44.7 µg, 0.2 mmol, 2 equiv) were placed in a MW sealed vial under argon atmosphere. Et_3N (250 µL) was added. The vial was kept in ultrasound bath until system became indiscrete. The resulting mixture was heated at 95 ºC (reflux) for 16 h, then allowed to cool to room temperature. The title product was obtained after flash chromatography (cyclohexane/EtOAc 3 : 1 to 1 : 1) as a yellow oil (19.9 mg, 0.05 mmol, yield = 50%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.95 (br s, 1H), 7.26 (d, *J* = 8.8 Hz, 1H), 7.10 (d, *J* = 2.4 Hz, 1H), 7.06 (d, *J* = 2.4, 1H), 6.87 (dd, *J* = 8.8, 2.4 Hz, 1H), 6.13 (t, *J* = 2.3 Hz, 1H), 3.88 (s, 3H), 3.73 – 3.65 (m, 2H), 2.98 (dd, *J* = 8.9, 6.5 Hz, 2H), 2.72 – 2.65 (m, 2H), 2.48 – 2.43 (m, 2H), 0.94 (s, 9H), 0.12 (s, 6). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 174.6, 154.1, 131.3, 129.1, 127.8, 122.6, 119.1, 112.6, 112.4, 11.9, 100.4, 55.9, 40.9, 28.9, 25.6 (3C), 22.5, 19.8, 18.2, -5.4 (2C). **HRMS** (ESI+) *m/z* calc. for $C_{22}H_{32}N_2O_3SiNa^+$ $[M+Na]^+$: 423.2074, found: 423.2068.

2. Substrate optimization for transfer of chirality during the tandem double condensation / Claisen rearrangement

General procedure for preparation of aldehyde

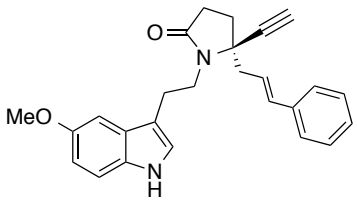
In a dry sealed MW vial, 5-methoxytryptamine (40 mg, 0.21 mmol, 1.05 equiv) was suspended in triethylamine (1 mL) and methyl oxoester **74** (0.2 mmol, 1 equiv) was added as a solution in toluene (0.5 mL) under inert atmoshere. The mixture heated at 95 ºC (reflux) for 16 h, then cooled to room temperature and the solvents evaporated. The resulting crude oil was dissolved in EtOAc (15 mL) and 0.5 M of HCl (10 mL) was added and the biphasic mixture stirred vigorously at 25 ºC for 20 min. The resulting crude oil purified by preparative TLC eluting with EtOAc.

Note: the aldehydes are unstable on HPLC.

General procedure for preparation of alkyne

K_2CO_3 (41.4 mg, 0.3 mmol, 2 equiv) was added to a solution of aldehyde **75** (0.15 mmol, 1 equiv) in methanol (0.5 mL) at 25 ºC and Bestmann-Ohira reagent (33 mg, 0.17 mmol, 1.15 equiv) in methanol (2 mL) was added dropwise at 0 ºC. The mixture was stirred at 25 ºC for 4 h. The volatiles were evaporated and the resulting crude material was purified by preparative TLC eluting with EtOAc/cyclohexane 1 : 1.

(*R*)-5-cinnamyl-5-ethynyl-1-(2-(5-methoxy-1*H*-indol-3-yl)ethyl)pyrrolidin-2-one (78b)

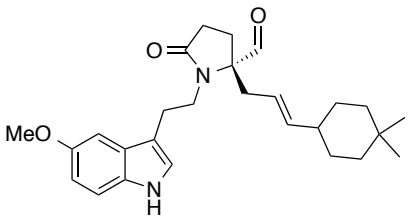


Off-white viscous oil, 64% (over 2 steps).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.89 (br s, 1H), 7.37 – 7.28 (m, 4H), 7.29 – 7.21 (m, 3H), 7.06 (d, *J* = 2.4 Hz, 1H), 6.87 (dd, *J* = 8.8, 2.4 Hz, 1H), 6.51 (d, *J* = 15.8 Hz, 1H), 6.14 (dt, *J* = 15.8, 7.3 Hz, 1H), 3.90 (s, 3H), 3.71 – 3.55 (m, 2H), 3.23 (ddd, *J* = 15.8, 10.4, 5.4 Hz, 1H), 3.13 (ddd, *J* = 13.9, 10.8, 6.2 Hz, 1H), 2.76 (ddd, *J* = 13.8, 7.3, 1.4 Hz, 1H), 2.60 – 2.48 (m, 3H), 2.42 (ddd, *J* = 16.8, 9.3, 6.3 Hz, 1H), 2.30 (ddd, *J* = 12.9, 9.7, 6.3 Hz, 1H), 2.22 (ddd, *J* = 12.8, 9.2, 6.7 Hz, 1H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 174.8, 154.0, 136.7, 134.9, 131.4, 129.7, 128.6 (2C), 127.9, 127.7, 126.3 (2C), 122.7, 113.2, 112.4, 111.8, 100.8, 84.8, 73.4, 60.9, 55.9, 43.4, 42.0, 31.9, 29.5, 24.6. **HRMS** (ESI+) *m*/*z* calc. for $C_{26}H_{27}N_2O_2^+$ $[M+H]^+$: 399.2067, found: 399.2061. **HPLC**

(Chiralpak IA (250 mm × 4.6 mm), hexane/isopropanol 70 : 30, 1 mL/min) t_R(*minor*) 6.8 – 6.9 min, t_R (*major*) 8.0 – 8.1 min, 60% *ee*.

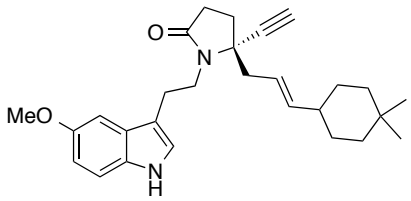
(S,*E*)-2-(2-(4,4-dimethylcyclohexyl)allyl)-1-(2-(5-methoxy-1*H*-indol-3-yl)ethyl)-5-oxopyrrolidine-2-carbaldehyde (75d)



Viscous brown oil, 81%. <u>*Note:*</u> the aldehyde is isolated as an inseparable 25 : 1 mixture of two compounds that seem isomeric and are presumably the *E* and *Z*-olefin isomers. The NMR data given below are for the major *E* isomer.

^{1}H NMR (500 MHz, $CDCl_3$) δ 9.26, (s, 1H), 8.00 (br s, 1H), 7.25 (d, *J* = 8.8 Hz, 1H), 7.15 (d, *J* = 2.4 Hz, 1H), 7.02 (d, *J* = 2.4 Hz, 1H), 6.86 (dd, *J* = 8.8, 2.4 Hz, 1H), 5.57 (ddt, *J* = 15.3, 6.9, 1.2 Hz, 1H), 5.22 (dddd, *J* = 15.6, 8.0, 6.9, 1.3 Hz, 1H), 3.90 (s, 3H), 3.67 (ddd, *J* = 13.8, 9.5, 6.0 Hz, 1H), 3.28, (ddd, *J* = 13.9, 9.3, 6.9 Hz, 1H), 3.10 – 2.98 (m, 2H), 2.81 – 2.40 (m, 4H), 2.06 (dt, *J* = 13.6, 8.3 Hz, 1H), 1.99 (dt, *J* = 13.6, 8.0 Hz, 1H), 1.88 – 1.80 (m, 1H), 1.52 – 1.45 (m, 2H), 1.40 – 1.33 (m, 2H), 1.27 – 1.13 (m, 4H), 0.90 (s, 3H), 0.86 (s, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 199.3, 176.2, 154.1, 142.9, 131.3, 127.8, 122.7, 119.0, 112.6, 112.6, 111.9, 100.3, 72.2, 55.9, 42.2 (2C), 40.8, 38.7, 34.8, 32.7, 29.7, 29.5, 28.7, 28.6, 24.8, 24.5, 24.0. **HRMS** (ESI+) *m/z* calc. for $C_{27}H_{36}N_2O_3Na^+$ $[M+Na]^+$: 495.2618, found: 459.2618.

(S,*E*)-5-(2-(4,4-dimethylcyclohexyl)allyl)-5-ethynyl-1-(2-(5-methoxy-1*H*-indol-3-yl)ethyl)pyrrolidin-2-one (78d)

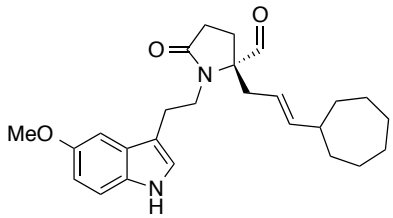


Off-white amorphous solid, 88%. <u>*Note:*</u> also isolated as an unseparable 25 : 1 mixture of presumed *E* and *Z*-olefin isomers. The NMR data given below are for the major *E* isomer. The solid was crystallized from CH_2Cl_2/pentane and melting point was measured on the crystalline material.

M.p. (CH_2Cl_2/pentane) 124-126 °C (70% *ee*). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.05 (br s, 1H), 7.27 – 7.24 (m, 2H), 7.05 (d, *J* = 2.4 Hz, 1H), 6.86 (dd, *J* = 8.8, 2.4 Hz, 1H), 5.56 (dd, *J* = 15.4, 6.8 Hz, 1H), 5.34 (dtd, *J* = 15.5, 7.2, 1.3 Hz, 1H), 3.89 (s, 3H), 3.62 (ddd, *J* = 13.8, 11.2, 5.8 Hz, 1H), 3.51 (ddd, *J* = 13.8, 11.3, 5.1 Hz, 1H), 3.19 (ddd, *J* = 13.9, 11.3, 5.1 Hz, 1H), 3.10 (ddd, *J* = 13.8, 11.3, 5.8 Hz, 1H), 2.57 – 2.45 (m, 3H), 2.44 – 2.35 (m, 2H), 2.26 (ddd, *J* = 12.8, 9.8, 6.6 Hz, 1H), 2.17 (ddd, *J* = 12.9, 9.4, 6.3 Hz,

1H), 1.91 – 1.80 (m, 1H), 1.55 – 1.47 (m, 2H), 1.41 – 1.34 (m, 2H), 1.30 – 1.13 (m, 4H), 0.90 (s, 3H), 0.86 (s, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) 174.7, 153.9, 142.3, 131.4, 127.9, 122.7, 120.1, 113.1, 112.2, 111.8, 100.8, 85.3, 72.9, 60.8, 55.9, 43.1, 41.9, 40.8, 38.7, 32.7, 31.5, 29.7, 29.6, 28.6, 28.6, 24.6 (2C), 24.5. **HRMS** (ESI−) *m*/*z* calc. for $C_{28}H_{35}N_2O_2^-$ $[M-H]^-$: 431.2704, found: 421.2703. **HPLC** (Chiralpak IA (250 mm × 4.6 mm), hexane/isopropanol/ethanol 80 : 15 : 5, 0.8 mL/min) t_R (*major*) 9.5 – 9.6 min, t_R (*minor*) 10.6 – 10.7 min, 70% *ee*.

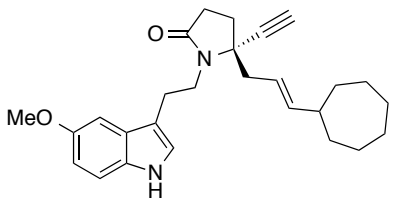
(S,*E*)-2-(2-cycloheptylallyl)-1-(2-(5-methoxy-1*H*-indol-3-yl)ethyl)-5-oxopyrrolidine-2-carbaldehyde (75e)



Viscous brown oil, 76%. <u>*Note:*</u> the aldehyde is isolated as an inseparable 15 : 1 mixture of two compounds that seem isomeric and are presumably the *E* and *Z*-olefin isomers. The NMR data given below are for the major *E* isomer.

^{1}H NMR (500 MHz, $CDCl_3$) δ 9.26, (s, 1H), 7.95 (br s, 1H), 7.25 (dd, *J* = 8.8, 0.6 Hz, 1H), 7.15 (d, *J* = 2.4 Hz, 1H), 7.02 (d, *J* = 2.4 Hz, 1H), 6.86 (dd, *J* = 8.8, 2.4 Hz, 1H), 5.59 (ddt, *J* = 15.3, 7.7, 1.3 Hz, 1H), 5.17 (dddd, *J* = 15.5, 7.9, 6.8, 1.2 Hz, 1H), 3.90 (s, 3H), 3.66 (ddd, *J* = 13.8, 9.5, 6.1 Hz, 1H), 3.29, (ddd, *J* = 13.9, 9.3, 6.9 Hz, 1H), 3.10 – 2.98 (m, 2H), 2.48 – 2.40 (m, 4H), 2.14 – 2.11 (m, 1H), 2.04 (dt, *J* = 13.6, 8.2 Hz, 1H), 1.97 (ddt, *J* = 13.6, 78.1 Hz, 1H), 1.72 – 1.54 (m, 6H), 1.53 – 1.39 (m, 4H), 1.33 – 1.23 (m, 2H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 199.3, 176.2, 154.1, 142.9, 131.2, 127.8, 122.7, 118.0, 112.6, 112.6, 111.9, 100.3, 72.2, 55.8, 43.0, 42.1 (2C), 34.7, 34.7, 34.6, 29.4, 28.2, 28.2, 26.1, 24.8, 24.0. **HRMS** (ESI−) *m*/*z* calc. for $C_{26}H_{33}N_2O_3^-$ $[M-H]^-$: 421.2497, found: 421.2497.

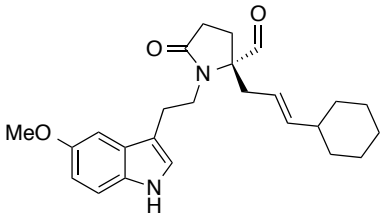
(S,*E*)-5-(2-cycloheptylallyl)-5-ethynyl-1-(2-(5-methoxy-1*H*-indol-3-yl)ethyl)pyrrolidin-2-one (78e)



Off-white amorphous solide, 87%. <u>*Note:*</u> also isolated as an unseparable 16 : 1 mixture of presumed *E* and *Z*-olefin isomers. The NMR data given below are for the major *E* isomer. The solid was crystallized from CH_2Cl_2/pentane and melting point were measured on the crystalline material (72% *ee*).

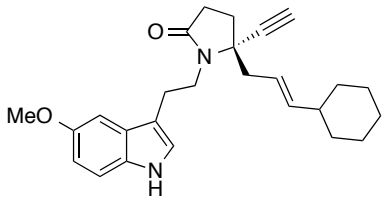
M.p. (CH_2Cl_2/pentane) 119-122 °C (72% *ee*). **^{1}H NMR** (500 MHz, $CDCl_3$) 7.92 (br s, 1H), 7.27 – 7.24 (m, 2H), 7.06 (d, *J* = 2.4 Hz, 1H), 6.87 (dd, *J* = 8.8, 2.4 Hz, 1H), 5.57 (ddt, *J* = 15.3, 7.6, 1.3 Hz, 1H), 5.29 (dtd, *J* = 15.4, 7.2, 1.2 Hz, 1H), 3.89 (s, 3H), 3.62 (ddd, *J* = 13.7, 11.2, 5.8 Hz, 1H), 3.51 (ddd, *J* = 13.8, 11.3, 5.2 Hz, 1H), 3.19 (ddd, *J* = 14.1, 11.5, 5.4 Hz, 1H), 3.09 (ddd, *J* = 13.9, 11.3, 5.7 Hz, 1H), 2.57 – 2.35 (m, 5H), 2.25 (ddd, *J* = 12.9, 9.8, 6.5 Hz, 1H), 2.20 – 2.09 (m, 2H), 1.75 – 1.55 (m, 6H), 1.53 – 1.40 (m, 4H), 1.34 – 1.24 (m, 2H). **^{13}C NMR** (126 MHz, $CDCl_3$) 174.7, 154.0, 143.3, 131.4, 127.9, 122.6, 119.2, 113.3, 112.3 111.8, 100.8, 85.3, 72.9, 60.9, 55.9, 43.0, 42.9, 41.8, 34.7, 34.7, 31.5, 29.6, 28.3 (2C), 26.2, 26.2, 24.5. **HRMS** (ESI−) *m*/*z* calc. for $C_{27}H_{33}N_2O_2^-$ $[M-H]^-$: 417.2548, found: 417.2544. **HPLC** (Chiralpak IA (250 mm × 4.6 mm), hexane/isopropanol/ethanol 80 : 15 : 5, 0.8 mL/min) t_R (*major*) 10.4 – 10.5 min, t_R (*minor*) 12.4 – 12.5 min, 72% *ee.*

(S,*E*)-2-(2-cyclohexylallyl)-1-(2-(5-methoxy-1*H*-indol-3-yl)ethyl)-5-oxopyrrolidine-2-carbaldehyde (75c)



Viscous brown oil, 91%. <u>*Note:*</u> the aldehyde is isolated as an inseparable 15 : 1 mixture of two compounds that seem isomeric and are presumably the *E* and *Z*-olefin isomers. The NMR data given below are for the major *E* isomer. **^{1}H NMR** (400 MHz, $CDCl_3$ δ 9.25, (s, 1H), 8.05 (br s, 1H), 7.25 (d, *J* = 8.8 Hz, 1H), 7.14 (d, *J* = 2.4 Hz, 1H), 7.01 (d, *J* = 2.3 Hz, 1H), 6.86 (dd, *J* = 8.8, 2.4 Hz, 1H), 5.54 (ddt, *J* = 15.3, 6.9, 1.3 Hz, 1H), 5.20 (dddd, *J* = 15.5, 8.0, 6.8, 1.3 Hz, 1H), 3.90 (s, 3H), 3.66 (ddd, *J* = 13.8, 9.3, 6.2 Hz, 1H), 3.28, (ddd, *J* = 13.8, 9.0, 7.1 Hz, 1H), 3.09 – 2.98 (m, 2H), 2.52 – 2.32 (m, 4H), 2.20 – 1.80 (m, 3H), 1.74 – 1.59 (m, 5H), 1.33 – 0.95 (m, 5H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 199.3, 176.2, 154.1, 143.1, 131.3, 127.8, 122.7, 118.8, 112.6, 112.6, 111.9, 100.3, 72.1, 55.8, 42.2 (2C), 40.8, 34.8, 32.8, 32.8, 29.5, 26.0, 25.9, 24.8, 24.0. **HRMS** (ESI+) *m/z* calc. for $C_{25}H_{32}N_2O_3Na^+$ $[M+Na]^+$: 431.2305, found: 431.2301.

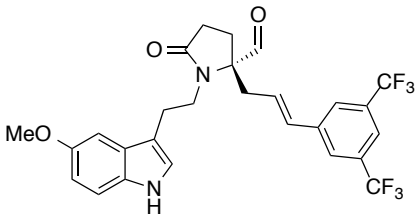
(S,*E*)-5-(2-cyclohexylallyl)-5-ethynyl-1-(2-(5-methoxy-1*H*-indol-3-yl)ethyl)pyrrolidin-2-one (78c)



Viscous pale yellow oil, 81%. *Note:* also isolated as an inseparable 15:1 mixture of presumed *E* and *Z*-olefin isomers. The NMR data given below are for the major *E* isomer.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.96 (br s, 1H), 7.27 – 7.24 (m, 2H), 7.06 (d, *J* = 2.4 Hz, 1H), 6.86 (dd, *J* = 8.8, 2.3 Hz, 1H), 5.56 (ddt, *J* = 15.4, 6.9, 1.2 Hz, 1H), 5.35 (dtd, *J* = 15.4, 7.1, 1.3 Hz, 1H), 3.89 (s, 3H), 3.62 (ddd, *J* = 13.7, 11.2, 5.8 Hz, 1H), 3.51 (ddd, *J* = 13.8, 11.3, 5.2 Hz, 1H), 3.19 (dddd, *J* = 13.8, 11.2, 5.2, 0.8 Hz, 1H), 3.09 (dddd, *J* = 13.9, 11.3, 5.8, 0.8 Hz, 1H), 2.56 – 2.44 (m, 3H), 2.44 − 2.35 (m, 2H), 2.25 (ddd, *J* = 12.8, 9.8, 6.5 Hz, 1H), 2.17 (ddd, *J* = 12.9, 9.4, 6.4 Hz, 1H), 1.99 – 1.89 (m, 1H), 1.75 – 1.61 (m, 5H), 1.33 – 0.99 (m, 5H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 174.7, 154.0, 142.5, 131.4, 127.9, 122.7, 119.9, 113.2, 112.3, 111.8, 100.8, 85.3, 72.9, 60.8, 55.9, 43.3, 41.8, 40.8, 32.8, 32.8, 31.5, 29.6, 26.1, 25.9, 24.5 (2C). **HRMS** (ESI+) *m*/*z* calc. for $C_{26}H_{32}N_2O_2Na^+$ $[M+Na]^+$: 427.2356, found: 427.2357. **HPLC** (Chiralpak IA (250 mm × 4.6 mm), hexane/isopropanol 80 : 20, 1 mL/min) t_R (*major*) 7.9 – 8.0 min, t_R (*minor*) 8.9 – 9.0 min, 70% *ee*.

(*S*,*E*)-2-(3-(3,5-bis(trifluoromethyl)phenyl)allyl)-1-(2-(5-methoxy-1*H*-indol-3-yl)ethyl)-5-oxopyrrolidine-2-carbaldehyde (75g)

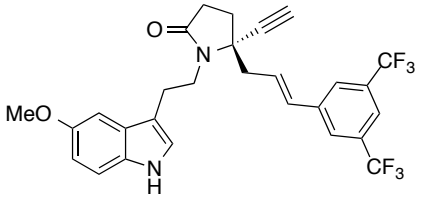


Viscous brown oil, 81%. *Note:* the aldehyde is isolated as an inseparable 8 : 1 mixture of two compounds that seem isomeric and are presumably the *E* and *Z*-olefin isomers. The NMR data given below are for the major *E* isomer.

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.25 (s, 1H), 7.94 (br s, 1H), 7.75 (s, 1H), 7.69 (s, 2H), 7.26 (d, *J* = 8.8 Hz, 1H), 7.13 (d, *J* = 2.5 Hz, 1H), 7.04 (d, *J* = 2.5 Hz, 1H), 6.87 (dd, *J* = 8.8, 2.4 Hz, 1H), 6.55 (d, *J* = 15.8 Hz, 1H), 6.14 (dt, *J* = 15.5, 7.4, Hz, 1H), 3.90 (s, 3H), 3.75 (ddd, *J* = 14.6, 9.3, 5.8 Hz, 1H), 3.35 (ddd, *J* = 15.2, 9.0, 6.5 Hz, 1H), 3.16 – 3.00 (m, 2H), 2.76 (ddd, *J* = 14.7, 7.7, 1.1 Hz, 1H), 2.61 (ddd, *J* = 14.5, 7.0, 1.3 Hz, 1H), 2.48 (dt, *J* = 9.4, 7.2 Hz, 2H), 2.13 (ddd, *J* = 13.8, 9.8, 6.8 Hz, 1H), 2.03 (ddd, *J* = 13.7, 9.4, 7.1 Hz, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 199.4, 175.8, 154.8, 144.1, 132.8,

132.1 (q, *J* = 33.5 Hz, 2C), 131.3, 127.4. 126.4, 126.0 (m, 2C), 122.8, 121.2 (m), 112.7, 112.3, 112.0, 100.3, 71.7, 55.9, 42.2, 35.3, 29.2, 24.7, 24.4. Note: signals of CF_3 group were not detected due to low intensity and high splitting. **HRMS** (ESI−) *m*/*z* calc. for $C_{27}H_{23}F_6N_2O_3^-$ $[M-H]^-$: 537.1618, found: 537.1608

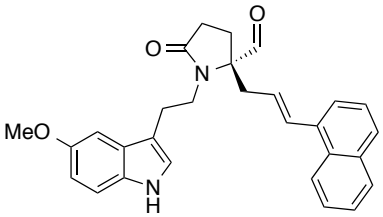
(*S*,*E*)-5-(3-(3,5-bis(trifluoromethyl)phenyl)allyl)-5-ethynyl-1-(2-(5-methoxy-1*H*-indol-3-yl)ethyl)pyrrolidin-2-one (78g)



Viscous pale yellow oil, 81%.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.95 (br s, 1H), 7.74 (s, 1H), 7.73 (s, 2H), 7.26 (d, *J* = 8.8 Hz, 1H), 7.23 (d, *J* = 2.5 Hz, 1H), 7.07 (d, *J* = 2.4 Hz, 1H), 6.87 (dd, *J* = 8.8, 2.4 Hz, 1H), 6.54 (d, *J* = 15.9 Hz, 1H), 6.30 (dt, *J* = 15.8, 7.4 Hz, 1H), 3.89 (s, 3H), 3.70 – 3.56 (m, 2H), 3.21 (ddd, *J* = 15.5, 10.1, 5.7 Hz, 1H), 3.14 (ddd, *J* = 14.0, 10.2, 6.6 Hz, 1H), 2.79 (ddd, *J* = 13.8, 7.0, 1.5 Hz, 1H), 2.59 −2.39 (m, 4H), 2.33 (ddd, *J* = 12.8, 9.6, 6.2 Hz, 1H), 2.18 (ddd, *J* = 12.8, 9.2, 6.7 Hz, 1H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 174.6, 154.1, 138.7, 132.2, 132.1 (q, *J* = 33.5 Hz, 2C), 131.4, 127.9, 127.3, 126.0 (m, 2), 122.7, 121.1 (m), 113.1, 112.3, 111.9, 100.9, 84.2, 73.9, 60.6, 55.9, 43.3, 42.0, 32.1, 29.4, 24.6. Note: signals of CF_3 group were not detected due to low intensity and high splitting. **HRMS** (ESI+) *m*/*z* calc. for $C_{28}H_{24}F_6N_2O_2Na^+$ $[M+Na]^+$: 557.1634, found: 557.1629. **HPLC** (Chiralpak IA (250 mm × 4.6 mm), hexane/isopropanol 85 : 15, 0.7 mL/min) t_R (*major*) 14.0 – 14.1 min, t_R (*minor*) 15.6 – 15.7 min, 37% *ee*.

(S,*E*)-1-(2-(5-methoxy-1*H*-indol-3-yl)ethyl)-2-(2-(naphthalen-1-yl)allyl)-5-oxopyrrolidine-2-carbaldehyde (75h)

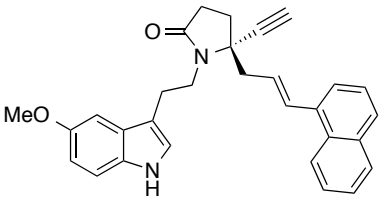


Viscous brown oil, 74%. Note: the aldehyde is isolated as an inseparable 13 : 1 mixture of two compounds that seem isomeric and are presumably the *E* and *Z*-olefin isomers. The NMR data given below are for the major *E* isomer.

^{1}H NMR (500 MHz, $CDCl_3$) δ 9.32 (s, 1H), 8.05 – 8.00 (m, 1H), 7.93 (br s, 1H), 7.88 – 7.83 (m, 1H), 7.79 (d, *J* = 7.9 Hz, 1H), 7.52 – 7.24 (m, 4H), 7.30 – 7.24 (m, 2H), 7.17 (d, *J* = 2.5 Hz, 1H), 7.04 (d, *J* = 2.5 Hz, 1H), 6.88 (dd, *J* = 8.8, 2.4 Hz, 1H), 6.02 (ddd, *J* = 15.2, 8.1, 6.8 Hz, 1H), 3.90 (s, 3H), 3.76 (ddd, *J* = 14.0, 9.3, 6.1 Hz, 1H), 3.43 (ddd, *J* = 13.9, 9.1, 6.8 Hz, 1H), 3.11 (dt, *J* = 9.2, 6.0 Hz, 2H), 2.82 (ddd, *J* = 14.7, 6.7, 1.5 Hz,

2H), 2.53 – 2.47 (m, 2H), 2.15 (ddd, *J* = 9.9, 7.7, 2.7 Hz, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 199.9, 176.0, 154.2, 134.3, 133.5, 133.0, 131.2, 130.9, 128.6, 128.2, 127.8, 126.2, 125.9, 125.6, 124.9, 123.9, 123.5, 122.7, 112.7, 112.5, 112.0, 100.3, 72.1, 55.9, 42.3, 35.6, 29.4, 24.8, 24.4. **HRMS** (ESI+) *m/z* calc. for $C_{30}H_{33}N_2O_4^+$ $[M+MeOH+H]^+$: 485.2435, found: 485.2434.

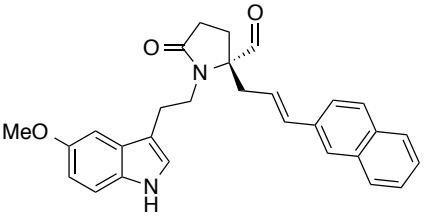
(S,*E*)-5-ethynyl-1-(2-(5-methoxy-1*H*-indol-3-yl)ethyl)-5-(2-(naphthalen-1-yl) allyl)pyrrolidin-2-one (78h)



Viscous off-white oil, 82%.

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.09 – 8.02 (m, 1H), 7.91 – 7.83 (m, 2H), 7.79 (d, *J* = 8.1 Hz, 1H), 7.55 – 7.48 (m, 3H), 7.46 – 7.42 (m, 1H), 7.30 – 7.22 (m, 3H), 7.07 (d, *J* = 2.4 Hz, 1H), 6.88 (dd, *J* = 8.8, 2.4 Hz, 1H), 6.17 (dt, *J* = 15.1, 7.3 Hz, 1H), 3.89 (s, 3H), 3.75 – 3.60 (m, 2H), 3.25 (ddd, *J* = 14.3, 10.5, 5.4 Hz, 1H), 3.17 (ddd, *J* = 14.1, 10.6, 6.5 Hz, 1H), 2.89 (ddd, *J* = 13.7, 7.3, 1.4 Hz, 1H), 2.67 (ddd, *J* = 13.8, 7.4, 1.4 Hz, 1H), 2.61 – 2.42 (m, 3H), 2.37 (ddd, *J* = 12.8, 9.5, 6.2 Hz, 1H), 2.31 (ddd, *J* = 12.8, 9.2, 6.9 Hz, 1H) **^{13}C NMR** (126 MHz, $CDCl_3$) 174.8, 154.0, 140.0, 134.6, 133.6, 132.3, 131.4, 131.0, 128.6, 128.1, 126.1, 126.1, 125.8, 125.6, 124.0, 123.6, 122.7, 113.2, 112.3, 111.8, 100.8, 84.8, 73.5, 60.9, 55.9, 43.8, 42.0, 32.0, 29.5, 24.6. **HRMS** (ESI+) *m/z* calc. for $C_{30}H_{29}N_2O_2^+$ $[M+H]^+$: 449.2224, found: 449.2225. **HPLC** (Chiralpak IA (250 mm × 4.6 mm), hexane/isopropanol 85 : 15, 1 mL/min) t_R (*major*) 7.1 – 7.2 min, t_R (*minor*) 9.3 – 9.4 min, 36% *ee*.

(S,*E*)-1-(2-(5-methoxy-1*H*-indol-3-yl)ethyl)-2-(2-(naphthalen-2-yl)allyl)-5-oxopyrrolidine-2-carbaldehyde (75i)

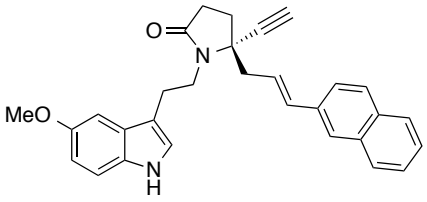


Viscous brown oil, 86%. <u>*Note:*</u> also isolated as an inseparable 14 : 1 mixture of presumed *E* and *Z*-olefin isomers. The NMR data given below are for the major *E* isomer.

^{1}H NMR (500 MHz, $CDCl_3$ δ 9.31 (s, 1H), 7.99 (br s, 1H), 7.81 – 7.76 (m, 3H), 7.66 (br s, 1H), 7.53 – 7.42 (m, 3H), 7.26 (d, *J* = 8.8 Hz, 1H), 7.17 (d, *J* = 2.4 Hz, 1H), 7.03 (d, *J* = 2.4 Hz, 1H), 6.88 (dd, *J* = 8.8, 2.4 Hz, 1H), 6.68 (d, *J* = 15.7 Hz, 1H), 6.11 (ddd, *J* = 15.7, 8.1, 6.7 Hz, 1H), 3.90 (s, 3H), 3.74 (ddd, *J* = 13.8, 9.0, 6.5 Hz, 1H), 3.42 (ddd, *J* = 13.9, 8.8, 7.2 Hz, 1H), 3.13 – 3.06 (m, 2H), 2.78 – 2.67 (m, 2H), 2.52 – 2.44 (m,

2H), 2.14 – 2.05 (m, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 199.0, 176.1, 15.2, 135.6, 133.9, 133.5, 133.0, 131.3, 128.3, 128.0, 127.8, 127.7, 126.4, 126.1 126.0, 123.3, 122.8, 121.9, 112.6, 112.4, 112.0, 100.4, 72.1, 55.9, 42.3, 35.4, 29.3, 24.8, 24.3. **HRMS** (ESI+) *m/z* calc. for $C_{30}H_{33}N_2O_4^+$ $[M+MeOH+H]^+$: 485.2435, found: 485.2434.

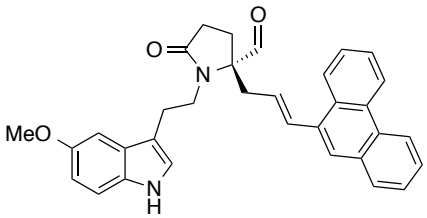
(S,*E*)-5-ethynyl-1-(2-(5-methoxy-1*H*-indol-3-yl)ethyl)-5-(2-(naphthalen-2-yl) allyl)pyrrolidin-2-one (78i)



Pale yellow oil, 79%.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.92 (br s, 1H), 7.82 – 7.77 (m, 3H), 7.69 (s, 1H), 7.55 (dd, *J* = 8.5, 1.8 Hz, 1H), 7.51 – 7.43 (m, 2H), 7.30 – 7.24 (m, 2H), 7.06 (d, *J* = 2.4 Hz, 1H), 6.88 (dd, *J* = 8.8, 2.4 Hz, 1H), 6.67 (d, *J* = 15.8 Hz, 1H), 6.27 (dt, *J* = 15.7, 7.3 Hz, 1H), 3.90 (s, 3H), 3.73 – 3.58 (m, 2H), 3.25 (ddd, *J* = 14.2, 10.7, 5.3 Hz, 1H), 3.15 (ddd, *J* = 14.1, 10.9, 5.9 Hz, 1H), 2.82 (ddd, *J* = 13.9, 7.3, 1.4 Hz, 1H), 2.62 (ddd, *J* = 13.9, 7.3, 1.4 Hz, 1H), 2.58 – 2.50 (m, 2H), 2.45 (ddd, *J* = 16.8, 9.2, 6.2 Hz, 1H), 2.33 (ddd, *J* = 12.9, 9.6, 6.3 Hz, 1H), 2.25 (ddd, *J* = 12.8, 9.2, 6.7 Hz, 1H) **^{13}C NMR** (126 MHz, $CDCl_3$) δ 174.8, 154.0, 135.0, 134.1, 133.5, 133.0, 131.4, 128.3, 127.9, 127.9, 127.7, 126.3, 126.2, 125.9, 123.4, 123.1, 122.7, 113.2, 112.3, 111.8, 100.8, 84.8, 73.4, 60.9, 55.9, 43.6, 42.0, 31.9, 29.5, 24.6. **HRMS** (ESI+) *m/z* calc. for $C_{30}H_{28}N_2O_2Na^+$ $[M+Na]^+$: 471.2043, found: 471.2044. **HPLC** (Chiralpak IA (250 mm × 4.6 mm), hexane/isopropanol 70 : 30, 1 mL/min) t_R (*major*) 9.5 – 9.6 min, t_R (*minor*) 11.2 – 11.3 min, 60% *ee*.

(S,*E*)-1-(2-(5-methoxy-1*H*-indol-3-yl)ethyl)-5-oxo-2-(2-(phenanthren-9-yl) allyl)pyrrolidine-2-carbaldehyde (75j)

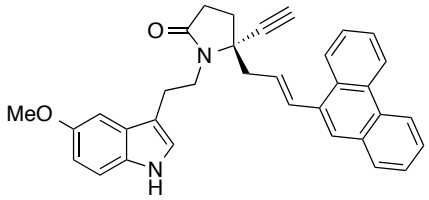


Brown gum, 78%. <u>*Note:*</u> also isolated as an inseparable 16 : 1 mixture of presumed *E* and *Z*-olefin isomers. The NMR data given below are for the major *E* isomer.

^{1}H NMR (500 MHz, $CDCl_3$) δ 9.34 (s, 1H), 8.73 (d, *J* = 7.9 Hz, 1H), 8.66 (d, *J* = 8.0 Hz, 1H), 8.05 (dd, *J* = 8.2, 1.3 Hz, 1H), 7.94 (br s, 1H), 7.87 (dd, *J* = 7.8, 1.5 Hz, 1H), 7.71 – 7.58 (m, 5H), 7.29 – 7.24 (m, 2H), 7.19 (d, *J* = 2.4 Hz, 1H), 7.04 (d, *J* = 2.4 Hz, 1H), 6.88 (dd, *J* = 8.8, 2.4 Hz, 1H), 6.10 (dd, *J* = 15.1, 8.0, 6.7 Hz, 1H), 3.90 (s, 3H), 3.84 – 3.76 (m, 1H), 3.45 (ddd, *J* = 13.9, 9.3, 6.6 Hz, 1H), 3.12 (td, *J* = 8.7, 6.4 Hz, 2H),

2.86 (ddd, *J* = 14.6, 8.1, 1.3 Hz, 1H), 2.79 (ddd, *J* = 14.7, 6.8, 1.6 Hz, 1H), 2.53 (td, *J* = 8.2, 4.5 Hz, 2H), 2.23 – 2.14 (m, 2H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ199.9, 173.0, 154.2, 133.5, 133.3, 131.6, 131.3, 130.3, 130.3, 130.2, 128.7, 127.8, 126.9, 126.7, 126.7, 126.6, 125.3, 124.9, 124.3, 123.1, 122.7, 122.5, 112.7, 112.5 112.0, 100.4, 72.9, 55.9, 42.3, 35.6, 29.4, 24.9, 24.5. **HRMS** (ESI+) *m/z* calc. for $C_{34}H_{35}N_2O_4^+$ $[M+MeOH+H]^+$: 535.2591, found: 535.2589.

(S,*E*)-5-ethynyl-1-(2-(5-methoxy-1*H*-indol-3-yl)ethyl)-5-(3-(phenanthren-9-yl)allyl)pyrrolidin-2-one (78j)

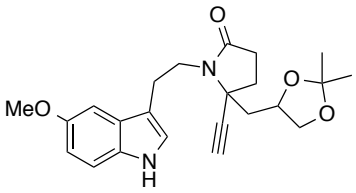


Viscous pale yellow oil, 90%.

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.74 (d, *J* = 7.5 Hz, 1H), 8.67 (d, *J* = 8.1 Hz, 1H), 8.10 (dd, *J* = 8.2, 1.1 Hz, 1H), 7.90 (br s, 1H), 7.86 (d, *J* = 2.5 Hz, 1H), 7.74 (s, 1H), 7.71 – 7.56 (m, 4H), 7.29 (d, *J* = 2.5 Hz, 1H), 7.28 – 7.23 (m, 2H), 7.08 (d, *J* = 2.4 Hz, 1H), 6.88 (dd, *J* = 8.8, 2.4 Hz, 1H), 6.26 (dt, *J* = 15.4, 7.3 Hz, 1H), 3.90 (s, 3H), 3.76 – 3.64 (m, 2H), 3.27 (ddd, *J* = 15.7, 10.6, 5.2 Hz, 1H), 3.19 (ddd, *J* = 14.0, 10.6, 6.7 Hz, 1H), 2.93 (ddd, *J* = 13.7, 7.3, 1.4 Hz, 1H), 2.69 (ddd, *J* = 13.7, 7.3, 1.4 Hz, 1H), 2.62 – 254 (m, 2H), 2.50 (ddd, *J* = 14.0, 9.1, 6.2 Hz, 1H), 2.41 (ddd, *J* = 12.8, 9.5, 6.1 Hz, 1H), 2.34 (ddd, *J* = 12.8, 9.1, 7.0 Hz, 1H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 174.7, 154.1, 133.6, 132.9, 131.7, 131.4, 130.4, 130.3, 130.2, 128.6, 127.9, 126.8, 126.7, 126.6, 126.6, 126.5, 124.9, 124.5, 123.1, 122.7, 122.5, 113.2, 112.3, 111.8, 100.8, 84.8, 73.8, 61.0, 55.9, 43.8, 42.1, 32.2, 29.6, 24.7. **HRMS** (ESI+) *m/z* calc. for $C_{34}H_{30}N_2O_2Na^+$ $[M+Na]^+$: 521.2199, found: 521.2199. **HPLC** (Chiralpak IA (250 mm × 4.6 mm), hexane/isopropanol 70 : 30, 1 mL/min) t_R (*major*) 10.6 – 10.7 min, t_R (*minor*) 12.2 – 12.3 min, 60% *ee*.

3. Initial cyclopropanation strategy

(±)--5-((2,2-dimethyl-1,3-dioxolan-4-yl)methyl)-5-ethynyl-1-(2-(5-methoxy-1H-indol-3-yl)ethyl)pyrrolidin-2-one (82)



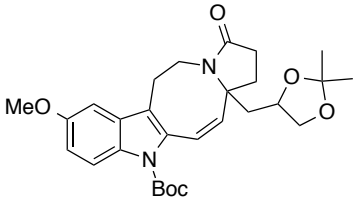
In a round-bottom flask, **78a** (1.27 g, 3.94 mmol, 1 equiv) was dissolved in acetone (15 mL) and NMO (924 mg, 7.88 mmol, 2 equiv) and a freshly prepared solution of OsO_4 (5 mg/mL, 6 mL, 30 mg, 0.118 mmol, 3 mol %) were added. The mixture was stirred vigorously at 25 ºC for 16 h. Then the mixture was quenched by addition of brine (50 mL), diluted with EtOAc (100 mL). The aqueous layer was extracted with EtOAc (2 × 100 mL) and the combined organic layers were washed with saturated solution of $Na_2S_2O_3$ (50 mL), and brine (50 mL), dried over $MgSO_4$, filtered and concentrated under reduced pressure. The crude diol was isolated as an brownish oil. It was then redissolved in dry acetone (10 mL), PTSA (37.4 mg, 0.197 mmol, 0.05 equiv) and Na_2SO_4 (1.12 g, 7.88 mmol, 2 equiv) were added in one portion to the vigorously stirred solution 25 ºC under Ar atmosphere. Stirring was continued for 2 h upon which time all diol had been converted to the acetonide (monitored by TLC). The volatiles were evaporated and the resulting crude mixture was dissolved in the minimum amount of CH_2Cl_2 and purified by column chromatography on silica gel eluting with cyclohexane/EtOAc 5 : 1 to 1 : 3 to afford the title compound as a pale yellow (790 mg, 1.99 mmol, yield = 51% or 82% based on recovered olefin) as well as 490 mg of starting material **78a**.

Note: acetonide was isolated as a mixture of two diasteriomers. NMR data is given for the mixture.

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.15 (br s, 1H *major* + 1H *minor*), 7.25 (d, *J* = 2.4 Hz, 1H *major* + 1H *minor*), 7.22 (d, *J* = 2.4 Hz, 1H *minor*), 7.18 (d, *J* = 2.4 Hz, 1H *major*), 7.04 (d, *J* = 2.4 Hz, 1H *minor*), 7.01 (d, *J* = 2.4 Hz, 1H *major*), 6.86 (dd, *J* = 8.7, 2.4 Hz, 1H *major* + 1H *minor*), 4.30 (dddd, *J* = 8.3, 7.2, 6.1, 3.4 Hz, 1H *major*), 4.09 – 4.01 (m, 1H *major* + 1H *minor*), 3.93 (d, *J* = 8.0, 5.9 Hz, 1H *minor*), 3.88 (s, 3H *minor*), 3.88 (s, 3H *major*), 3.65 – 3.53 (m, 1H *major* + 1H *minor*), 3.53 – 3.40 (m, 2H *major* + 2H *minor*), 3.21 – 3.04 (m, 2H *major* + 2H *minor*), 2.56 – 2.30 (m, 5H *major* + 5H *minor*), 2.20 (dd, *J* = 14.6, 7.3 Hz, 1H *minor*), 1.92 (dd, *J* = 14.6, 4.1 Hz, 1H *minor*), 1.88 (dd, *J* = 13.7, 3.4 Hz, 1H *major*), 1.60 (dd, *J* = 13.7, 8.4 Hz, 1H *major*), 1.39 (s, 3H *minor*),

1.37 (s, 3H *major*), 1.35 (s, 3H *major*), 1.32 (s, 3H *minor*). **^{13}C NMR** (126 MHz, $CDCl_3$) δ175.2, 175.0, 154.0, 153.9, 131.4, 131.4, 127.9, 127.8, 122.8, 122.8, 113.0, 112.8, 112.3, 112.2, 111.9 (2C), 109.3, 109.2, 100.7, 100.6, 85.0, 83.9, 73.8, 73.2, 72.5, 71.6, 69.7, 69.6, 60.6, 59.6, 55.9 (2C), 43.0, 42.8, 41.9, 41.9, 32.9, 32.5, 29.6, 29.5, 25.8, 26.8, 26.8, 25.7, 24.6, 24.5. **HRMS** (ESI+) *m/z* calc. for $C_{23}H_{29}N_2O_4^+$ $[M+H]^+$: 397.2122, found: 397. 2109.

(±)-*tert*-Butyl-(*Z*)-13a-((2,2-dimethyl-1,3-dioxolan-4-yl)methyl)-8-methoxy-3-oxo-1,2,3,5,6,13a-hexahydro-11*H*-pyrrolo[1',2':1,8]azocino[5,4-*b*]indole-11-carboxylate (83)



In the glovebox, AuCl (22.4 mg, 0.1 mmol, 5 mol %) was added to a solution of **82** (780 mg, 1.97 mmol, 1 equiv) in anhydrous CH_2Cl_2 (5 mL) placed in a screw-cap vial. The mixture was stirred at 25 ºC for 5 h (monitored by TLC, full conversion) upon which time the product precipitated. The reaction was filtered through a short pad of silica gel washing thoroughly with acetone (*ca.* 500 mL). The solid was dried under high vacuum to obtain the cyclized product as a white solid (678.6 mg, 1.71 mmol, yield = 87%), which was used in following step without purification.

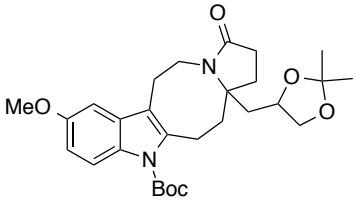
NaH (60% suspension in mineral oil, 103 mg, 2.56 mmol, 1.5 equiv) was added to a solution of tetracycle (678.6 mg, 1.71 mmol, 1 equiv) in anhydrous DMF (67 mL) at 0 ºC under argon atmosphere. After stirring at 0 ºC for 30 min, Boc anhydride (579 mg, 2.65 mmol, 1.55 equiv) was added and the resulting mixture was allowed to warm to 25 ºC and stirred for 1 h. Then the mixture was quenched by addition of a saturated aqueous solution of NH_4Cl (50 mL), diluted with EtOAc (100 mL) and brine (50 mL). The aqueous layer was extracted with EtOAc (2 × 100 mL) and the combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification by flash chromatography eluting with cyclohexane/EtOAc 4 : 1 to 2 : 1 gave the title product as a white solid (830 mg, 1.67 mmol, yield = 85% over 2 steps).

Note: The NMR data given below are for the major diasteriomer.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.91 (d, *J* = 9.0 Hz, 1H), 6.95 (d, *J* = 2.5 Hz, 1H), 6.88 (dd, *J* = 9.1, 2.6 Hz, 1H), 6.60 (d, *J* = 12.3 Hz, 1H), 5.54 (d, *J* = 12.3 Hz, 1H), 4.33 (tdd, *J* = 7.3, 5.9, 4.5 Hz, 1H), 4.14 (dd, *J* = 7.9, 5.9 Hz, 1H), 4.07 (td, *J* = 13.4, 4.2 Hz, 1H),

3.87 (s, 3H), 3.58 (t, *J* = 7.7 Hz, 1H), 3.08 (dd, *J* = 13.8, 4.6 Hz, 1H), 2.95 – 2.88 (m, 1H), 2.61 (td, *J* = 13.6, 4.9 Hz, 1H), 2.39 (ddd, *J* = 16.1, 12.3, 7.9 Hz, 1H), 2.20 – 2.08 (m, 3H), 2.07 – 1.95 (m, 2H), 1.66 (s, 9H), 1.43, (s, 3H), 1.38 (s, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 175.1, 156.0, 150.3, 134.0, 130.8, 129.5, 129.2, 120.7, 116.8, 116.4, 113.3, 109.3, 100.8, 83.8, 71.8, 70.6, 65.1, 55.6, 42.9, 36.2, 34.9, 29.1, 28.3 (3C), 26.9, 25.7, 22.4. **HRMS** (ESI+) *m/z* calc. for $C_{28}H_{36}N_2O_6Na^+$ $[M+Na]^+$: 519.2466, found: 519.2466.

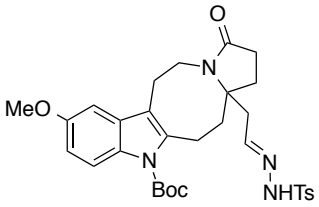
(±)-*tert*-Butyl-13a-((2,2-dimethyl-1,3-dioxolan-4-yl)methyl)-8-methoxy-3-oxo-1,2,3,5,6,12,13,13a-octahydro-11*H*-pyrrolo[1',2':1,8]azocino[5,4-*b*]indole-11-carboxylate (84)



Pd/C (10 ω% Pd/C, 24.9 mg, 0.02 mmol, 0.02 equiv) was placed in a dry flask and covered up with anhydrous methanol (10 mL) and the flask was placed under inert atmosphere. The tetracycle **86** (534 mg, 1.07 mmol, 1 equiv) was added and the mixture placed under 1 atm of hydrogen (2 sequences vacuum/hydrogen). It was then stirred vigorously at 25 ºC for 15 h. The solids were filtered off over Celite washing with acetone and the volatiles were removed under reduced pressure. Purification by flash chromatography eluting with cyclohexane/EtOAc 3 : 1 to 1 : 1 gave the title product as a white amorphous solid (437mg, 0.88 mmol, yield = 82%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.87 (d, *J* = 9.0 Hz, 1H), 6.87 (d, *J* = 2.6 Hz, 1H), 6.83 (dd, *J* = 9.0, 2.5 Hz, 1H), 4.18 – 4.09 (m, 2H), 4.02 (dd, *J* = 7.9, 5.9 Hz, 1H), 3.86 (s, 3H), 3.46 – 3.37 (m, 2H), 3.08 – 3.00 (m, 1H), 2.94 – 2.83 (m, 3H), 2.48 (ddd, *J* = 17.1, 9.9, 5.6 Hz, 1H), 2.39 (ddd, *J* = 17.1, 9.8, 7.3 Hz, 1H), 2.18 – 2.07 (m, 3H), 1.98 (ddd, *J* = 13.4, 10.0, 7.4 Hz, 1H), 1.79 (dd, *J* = 14.3, 8.7 Hz, 1H), 1.68 (s, 9H), 1.61 (dd, *J* = 14.4, 3.3 Hz, 1H) 1.36, (s, 3H), 1.32 (s, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 175.1, 156.0, 150.3, 134.0, 130.8, 129.5, 129.2, 120.7, 116.8, 116.4, 113.3, 109.3, 100.8, 83.8, 71.8, 70.6, 65.1, 55.6, 42.9, 36.2, 34.9, 29.1, 28.3 (3C), 26.9, 25.7, 22.4. **HRMS** (ESI+) *m/z* calc. for $C_{28}H_{38}N_2O_6Na^+$ $[M+Na]^+$: 521.2622, found: 521.2610.

(±)-*tert*-Buty(*E*)-8-methoxy-3-oxo-13a-(2-(2-tosylhydrazono)ethyl)-1,2,3,5,6,12,13,13a-octahydro-11*H*-pyrrolo[1',2':1,8]azocino[5,4-*b*]indole-11-carboxylate (85)

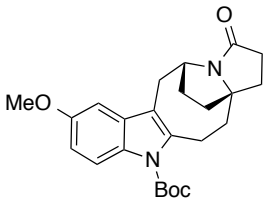


The acetonide **84** (380 mg, 0.77 mmol, 1 equiv) wass dissolved in MeOH/water 10 : 1 (11 mL) and PTSA (37.4 mg, 0.197 mmol, 0.05 equiv) was added in one portion to the vigorously stirred solution 25 ºC. Stirring was continued for 24 h upon which time all acetonide had been converted to the diol (monitored by TLC). All volatiles were removed under reduced pressure and crude diol was redissolved in acetone/water 2 : 1 (9 mL) and $NaIO_4$ (362.5 mg, 1.69 mmol, 2.2 equiv) was added in one portion to the vigorously stirred solution. Stirring was continued for 2 h upon which time all diol had been converted to the aldehyde (monitored by TLC). The suspension was then poured on 30 mL of brine and extracted with EtOAc (3 × 70 mL). The combined organic extracts were dried over Na_2SO_4 and concentrated *in vacuo*.

The mixture was redissolved in CH_2Cl_2 (4 mL) and $TsNHNH_2$ (144 mg, 0.77 mmol, 1 equiv) was added. The solution was stirred at 25 ºC for 15 min upon which time TLC showed full conversion of the aldehyde. The mixture was loaded on silica gel column and purified by chromatography eluting with cyclohexane/EtOAc 3:7 to 0:1 to afford the product as an off-white solid (358 mg, 0.60 mmol, *E*:*Z* = 100:9, yield from **84** = 78%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.69 (s, 1H), 7.86 (d, *J* = 9.0 Hz, 1H), 7.79 – 7.75 (m, 2H), 7.30 (d, *J* = 8.1 Hz, 2H), 7.02 (dd, *J* = 6.9, 4.9 Hz, 1H), 6.88 (d, *J* = 2.5 Hz, 1H), 6.84 (dd, *J* = 9.0, 2.6 Hz, 1H), 4.06 – 3.96 (m, 1H), 3.85 (s, 3H), 3.36 (dd, *J* = 17.0, 7.4 Hz, 1H), 3.10 – 2.78 (m, 4H), 2.54 (dd, *J* = 14.4, 4.9 Hz, 1H), 2.45 – 2.26 (m, 5H), 2.22 – 2.12 (m, 1H), 2.04 – 1.92 (m, 2H), 1.83 (t, *J* = 8.3 Hz, 2H), 1.68 (s, 9H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 175.7, 155.9, 150.7, 146.0, 144.1, 138.1, 135.5, 130.5, 129.9, 129.6 (2C), 127.9 (2C), 116.3, 115.5, 111.9, 100.4, 83.9, 65.6, 55.7, 41.4, 40.1, 38.6, 29.5, 28.8, 28.3 (3C), 23.0, 22.4, 21.6. **HRMS** (ESI–) *m/z* calc. for $C_{31}H_{38}N_4O_6S^-$ $[M+Na]^+$: 617.2404, found: 617.2422.

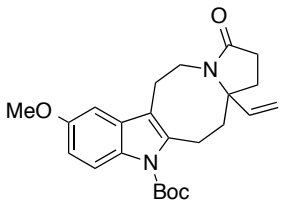
(±)-*tert*-Butyl-8-methoxy-3-oxo-2,3,5,6,12,13-hexahydro-1*H*,11*H*-5,13a-ethanopyrrolo[1',2':1,8]azocino[5,4-*b*]indole-11-carboxylate (88)



M.p. 179-181 ºC. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.01 (d, *J* = 8.9 Hz, 1H), 6.91 (d, *J* = 2.5 Hz, 1H), 6.88 (dd, *J* = 9.0, 2.6 Hz, 1H), 4.68 (t, *J* = 6.8 Hz, 1H), 3.90 (s, 3H), 3.48 (dt, *J* = 13.7, 3.3 Hz, 1H), 3.05 – 3.95 (m, 2H), 2.89 (d, *J* = 15.6 Hz, 1H), 2.83 (ddd, *J* = 16.4, 12.9, 7.4 Hz, 1H), 2.34 (dd, *J* = 16.4, 8.1 Hz, 1H), 2.15 – 2.02 (m, 3H), 1.84 – 1.69 (m, 11H), *1.60 −1.54 (m, 1H)*, 1.40 (dd, *J* = 20.6, 11.7 Hz, 1H), 1.02 – 0.94 (m, 1H). **^{13}C NMR** (126 MHz, $CDCl_3$) 177.6, 156.1, 150.3, 138.3, 131.3, 130.3, 116.7, 116.6, 111.9, 100.4, 83.7, 70.1, 56.8, 55.8, 39.7, 39.0, 38.5, 33.5, 30.3, 28.8, 28.3 (3C), 23.9. **HRMS** (ESI+) *m/z* calc. for $C_{24}H_{30}N_2O_4Na$ $[M+Na]^+$: 433.2098, found: 433.2092.

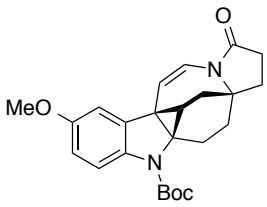
Note: the signal in "*" overlapping with signal of water.

(±)-*tert*-Butyl-8-methoxy-3-oxo-13a-vinyl-1,2,3,5,6,12,13,13a-octahydro-11*H*-pyrrolo[1',2':1,8]azocino[5,4-*b*]indole-11-carboxylate (89)



^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 (d, *J* = 8.9 Hz, 1H), 6.87 (d, *J* = 2.5 Hz, 1H), 6.84 (dd, *J* = 9.0, 2.6 Hz, 1H), 5.73 (dd, *J* = 17.4, 10.8 Hz, 1H), 5.10 (d, *J* = 10.8 Hz, 1H), 5.01 (d, *J* = 17.4 Hz, 1H), 4.26 – 4.16 (m, 1H), 3.86 (s, 3H), 3.42 (ddd, *J* = 16.0, 8.2, 2.6 Hz, 1H), 3.04 – 2.83 (m, 4H), 2.48 (ddd, *J* = 16.6, 9.0, 6.0 Hz, 1H), 2.38 (ddd, *J* = 16.8, 9.4, 7.2 Hz, 1H), 2.27 (ddd, *J* = 15.1, 9.1, 2.6 Hz, 1H), 2.17 (ddd, *J* = 15.3, 8.2, 2.9 Hz, 1H), 2.02 (ddd, *J* = 12.9, 9.1, 7.2 Hz, 1H), 1.93 (ddd, *J* = 12.8, 9.3, 6.0 Hz, 1H), 1.70 (s, 9H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 176.1, 155.9, 150.7, 140.8, 138.9, 130.7, 129.9, 116.8, 116.2, 113.9, 111.9, 100.4, 83.6, 67.3, 55.7, 41.2, 36.7, 32.4, 29.4, 28.4 (3C), 23.2, 22.0. **HRMS** (ESI+) *m/z* calc. for $C_{24}H_{30}N_2O_4Na$ $[M+Na]^+$: 433.2098, found: 433.2091.

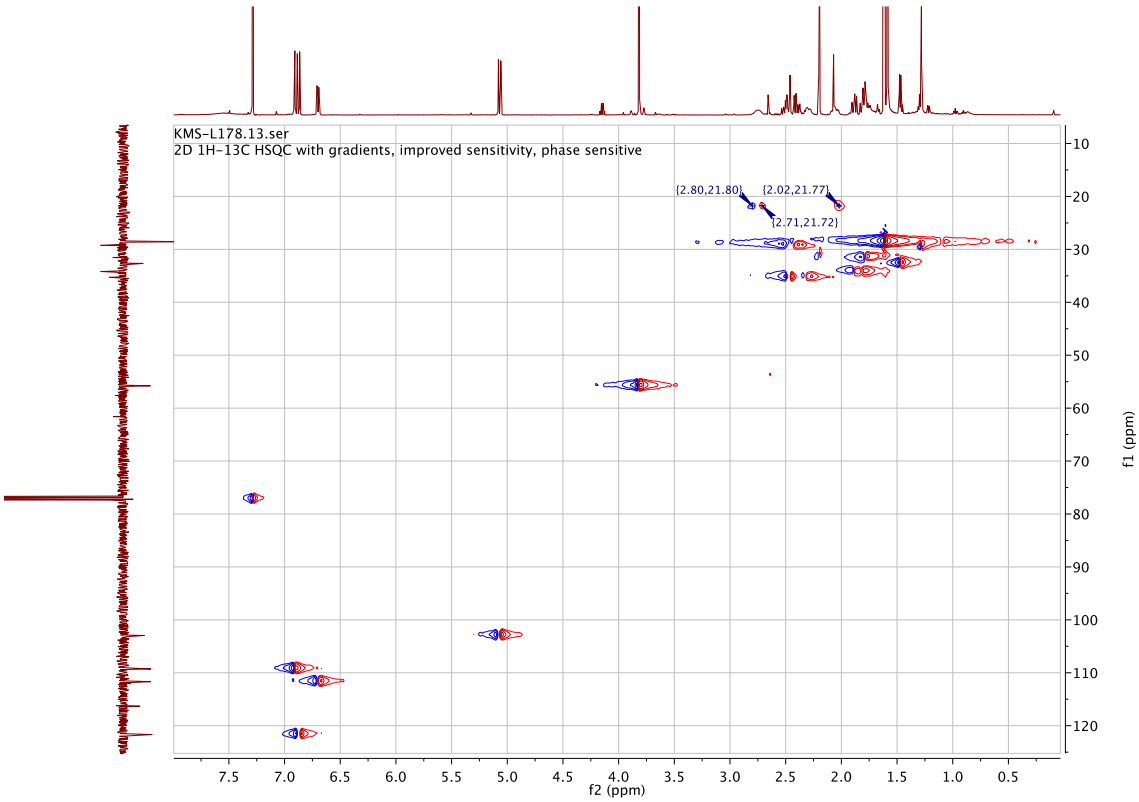
(±)-*tert*-Butyl-2-methoxy-9-oxo-5b,6,8,9-tetrahydro-5*H*,7*H*-5a,6a-ethanopyrrolo[1'',2'':1',7']azepino[4',5':2,3]cyclopropa[1,2-*b*]indole-5-carboxylate (91)



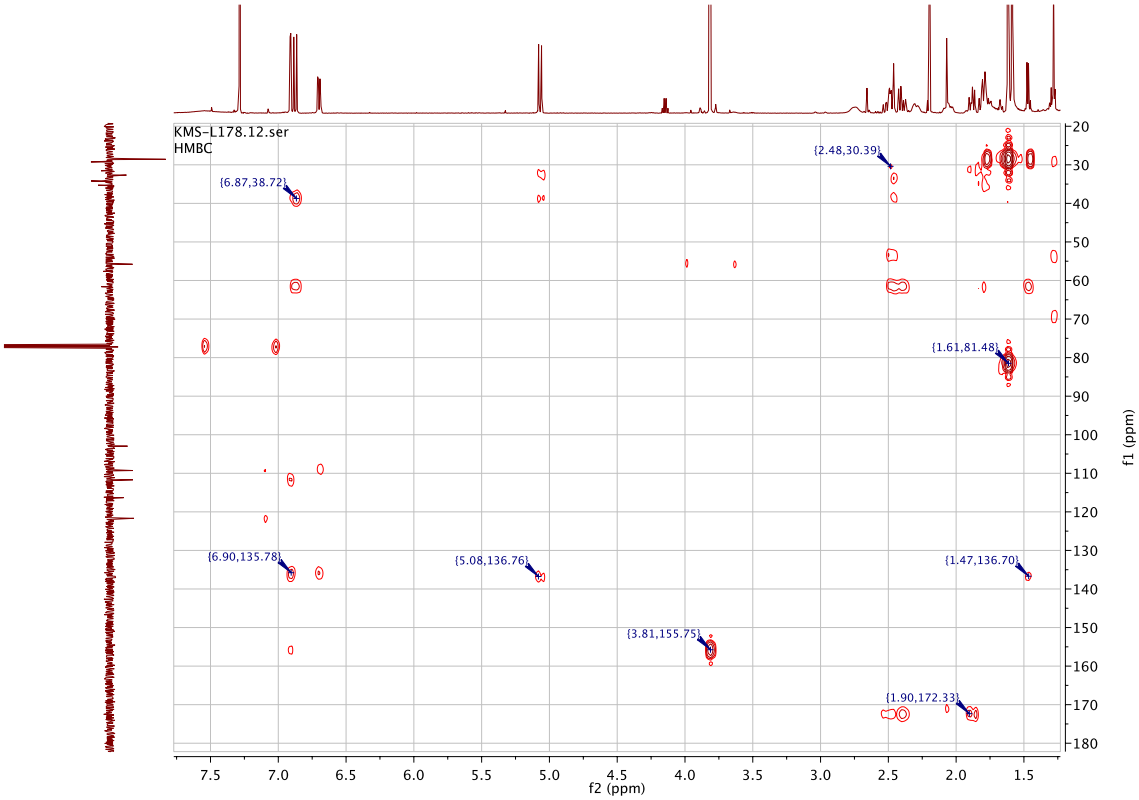
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 (br s, 1H), 6.89 (d, *J* = 2.7 Hz, 1H), 6.86 (d, *J* = 10.7 Hz, 1H), 6.68 (dt, *J* = 8.8, 2.7 Hz, 1H), 5.05 (d, *J* = 10.7 Hz, 1H), 3.80 (s, 3H), 2.74 (br d, *J* = 10.1 Hz, 1H), 2.54 – 2.43 (m, 2H), 2.39 (dd, *J* = 17.1, 8.3 Hz, 1H), 2.28 (dd, *J* = 15.0, 5.8 Hz, 1H), 2.08 −1.97 (m, 1H), 1.87 (dd, *J* = 12.5, 8.3 Hz, 1H), 1.84 – 1.72 (m, 3H), 1.60 (s, 9H), 1.46 (d, *J* = 5.8 Hz, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ *172.5*, *155.8*, 154.7, *136.7 *, *135.8*, 121.7, 116.3, 111.7, 109.3, 103.0, *81.5*, 61.6, 55.8, *38.8*, 35.3, 34.2, 32.7, 31.5, 29.2, *30.4*, 28.6 (3C), *21.8*.

Note: One quaternary carbon could not be detected; the signals between "*" were only observed or confirmed by 2D ^{13}C-^{1}H correlation (HMQC, HMBC see below).

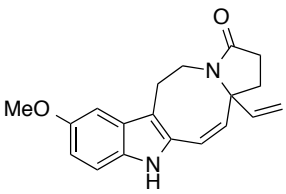
HSQC correlation for 91:



HMBC correlation for 91:



(±)-(*Z*)-8-Methoxy-13a-vinyl-1,2,5,6,11,13a-hexahydro-3*H*-pyrrolo[1',2':1,8]azocino[5,4-*b*]indol-3-one (98)

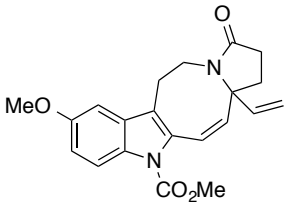


A solution of *n*-BuLi (0.25 M, 0.35 mL, 0.088 mmol, 0.97 equiv) was added over a solution of (±)-(*Z*,*E*)-**96** (50 mg, 0.091 mmol, 1 equiv) in anhydrous THF (9.6 mL) at –78 ºC in a sealed MW vial (20 mL volume) under argon atmosphere. The resulting mixture was kept stirring at –78 ºC for 30 min. The reaction was allowed to warm to room temperature and it was then heated at 130 ºC and kept stirring at that temperature for 30 h. After cooling to room temperature, the volatiles were removed under reduced pressure and the crude mixture was purified by preparative silica gel TLC eluting with cyclohexane/EtOAc 1 : 1 to afford (±)-**97** as a white solid (6.1 mg, 0.017 mmol, yield = 18%). (±)-**98** and (±)-**99** were also isolated (combined yield = 51%).

M.p. 238-240 ºC. **^{1}H NMR** (500 MHz, CD_2Cl_2) δ 7.93 (br s, 1H), 7.17 (d, *J* = 8.6 Hz, 1H), 6.96 (d, *J* = 2.4 Hz, 1H), 6.79 (dd, *J* = 8.7, 2.5 Hz, 1H), 6.48 (d, *J* = 12.4 Hz, 1H), 5.93 (dd, *J* = 17.4, 10.6 Hz, 1H), 5.63 (d, *J* = 12.4 Hz, 1H), 5.53 – 5.46 (m, 2H), 3.94

(td, *J* = 13.3, 4.6 Hz, 1H), 3.84 (s, 3H), 3.05 (dd, *J* = 13.5, 4.9 Hz, 1H), 2.93 (ddd, *J* = 14.3, 4.6, 1.8 Hz, 1H), 2.63 (td, *J* = 14.1, 5.3 Hz, 1H), 2.23 (ddd, *J* = 15.7, 12.0, 7.8 Hz, 1H), 2.12 – 1.98 (m, 3H). **^{13}C NMR** (126 MHz, CD_2Cl_2) δ 174.9, 154.6, 142.3, 133.3, 131.7, 131.5, 128.2, 119.6, 119.3, 112.9, 111.8, 111.0, 100.2, 68.7, 56.0, 38.7, 37.2, 29.4, 22.2. **HRMS** (ESI+) *m/z* calc. for $C_{19}H_{21}N_2O_2$ $[M+H]^+$: 309.1598, found: 309.1594.

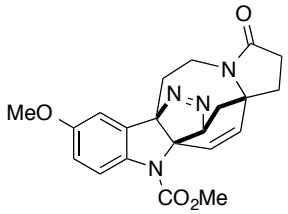
(±)-Methyl (*Z*)-8-methoxy-3-oxo-13a-vinyl-1,2,3,5,6,13a-hexahydro-11*H*-pyrrolo[1',2':1,8]azocino[5,4-*b*]indole-11-carboxylate (99)



M.p. 207-209 ºC. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.88 (dd, *J* = 9.1, 0.5 Hz, 1H), 6.93 (d, *J* = 2.5 Hz, 1H), 6.88 (dd, *J* = 9.0, 2.6 Hz, 1H), 6.75 (d, *J* = 12.5 Hz, 1H), 5.86 (dd, *J* = 17.7, 10.4 Hz, 1H), 5.66 (d, *J* = 12.5 Hz, 1H), 5.53 – 5.52 (m, 1H), 5.50 (dd, *J* = 5.3, 0.7 Hz, 1H), 4.02 (s, 3H), 3.93 (td, *J* = 13.4, 4.4 Hz, 1H), 3.87 (s, 3H), 3.03 (dd, *J* = 13.1, 5.3 Hz, 1H), 2.87 (ddd, *J* = 14.0, 4.4, 1.6 Hz, 1H), 2.56 (td, *J* = 13.8, 5.4 Hz, 1H), 2.39 (ddd, *J* = 16.1, 12.3, 7.9 Hz, 1H), 2.19 – 2.10 (m, 2H), 2.00 (td, *J* = 12.3, 8.1 Hz, 1H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 175.0, 156.2, 152.3, 141.9, 133.9, 130.5, 129.8, 128.0, 120.9, 119.3, 117.5, 116.5, 113.4, 100.9, 67.7, 55.6, 53.4, 37.0, 36.5, 29.1, 21.7. **HRMS** (ESI+) *m/z* calc. for $C_{21}H_{23}N_2O_4$ $[M+H]^+$: 367.1652, found: 367.1650.

4. Isolation of pyrazoline intermediate (±)-100:

(±)-Methyl (6a*R,11a*R**,13a*S**,15*R**)-8-methoxy-3-oxo-2,3,5,6-tetrahydro-1*H*,11*H*-6a,11a,13a-(epidiazenoethane[1,1,2]triyl)pyrrolo[1',2':1,8]azocino[5,4-*b*]indole-5-carboxylate ((±)-100)**



To a solution of (±)-(*Z*,*E*)-**96** (55 mg, 0.1 mmol, 1 equiv) in anhydrous CH_2Cl_2 (12 mL) in a sealed MW vial, was added $BF_3.OEt_2$ (25 µL, 0.2 mmol, 2 equiv). The mixture was stirred vigorously and heated at 50 ºC for 2 h. The resulting solution was allowed to cool to room temperature then filtered through a pad of silica gel washing with acetone (3 × 25 mL). The volatiles were removed under vacuum and the crude mixture was purified by preparative silica gel TLC eluting with EtOAc to afford the title product as an off-white crystalline solid (11.4 mg, 0.030 mmol, yield = 30% - contains *ca* 40 mol% of EtOAc). The compound was not dried further due to its high unstability towards heating and light and our attempts to do so resulted in its partial

decomposition into cyclopropane **48**. Careful purification and rapid handling were required to obtain data of the quality we present herein.

Note 1: this compound also decomposed readily in the presence of a base: typically, we did not observe the pyrazoline when the same reaction mixture was quenched with $NaHCO_3$.

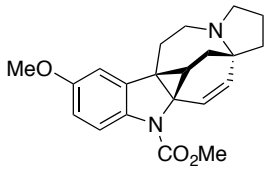
M.p. could not measured since compound decomposes to cyclopropane at temperature > 50 ºC.

This compound is rotameric at room temperature with low rotation barrier (broadening of spectrum). Cooling the solution at –20 ºC allowed us to resolve the two rotamers in an approximate 1 : 0.55 ratio. The NMR characterization below corresponds to the mixture of this two rotamers at – 20 ºC. **^{1}H NMR** (500 MHz, $CDCl_3$, 253K) δ 7.88 (d, *J* = 8.9 Hz, 1H *minor* rotamer), 7.45 (d, *J* = 8.9 Hz, 1H *major* rotamer), 7.13 (d, *J* = 2.7 Hz, 1H *major*), 7.12 (d, *J* = 2.7 Hz, 1H *minor*), 6.92 (dd, *J* = 8.9, 2.6 Hz, 1H *minor*), 6.89 (dd, *J* = 9.0, 2.6 Hz, 1H *major*), 6.09 (d, *J* = 9.8 Hz, 1H *major*), 6.03 (d, *J* = 10.1 Hz, 1H *minor*), 6.00 (dd, *J* = 12.7, 1.2 Hz, 1H *major*), 5.86 (dd, *J* = 12.6, 1.5 Hz, 1H *minor*), 5.82 (d, *J* = 9.8 Hz, 1H *major*), 5.76 (d, *J* = 9.7 Hz, 1H *minor*), 4.47 – 4.36 (m, 1H *major* + 1H *minor*), 3.90 (s, 3H *major*), 3.85 (s, 3H *major*), 3.85 (s, 3H *minor*), 3.84 (s, 3H *minor*), 2.82 – 2.75 (m, 1H *major* + 1H *minor*), 2.67 – 2.35 (m, 3H *major* + 3H *minor*), 2.24 – 2.12 (m, 2H *major* + 2H *minor*), 2.10 – 2.02 (m, 1H *major* + 1H *minor*), 1.99 – 1.84 (2H *major* + 2H *minor*). **^{13}C NMR** (126 MHz, $CDCl_3$, 253K) δ 173.4, 173.3, 156.2, 156.1, 153.2, 152.4, 135.2, 133.8, 132.8, 132.4, 132.2, 132.1, 126.8, 126.1, 115.9, 115.8, 115.7 (2C), 109.0, 108.9, 106.2, 105.1, 90.1, 89.7, 71.2, 70.9, 59.0, 58.8, 55.7 (2C), 53.2, 53.1, 35.0, 34.9, 33.5, 33.5, 33.2, 33.0, 29.6, 29.6, 28.0, 27.9. **HRMS** (ESI+) *m/z* calc. for $C_{21}H_{22}N_4O_4Na^+$ $[M+Na]^+$: 417.1533, found: 417.1533.

The structure of this compound was unambiguously confirmed by single crystal X-ray crystallography analysis (see below for more details). Solvent system for crystallization: acetone, ethyl acetate, dichloromethane, and cyclohexane.

5. Lundurine C from the double reduction of 48:

Methyl (5a*R,5b*S**,6a*S**,12a*R**)-2-methoxy-5b,6,8,9,11,12-hexahydro-5*H*,7*H*-5a,6a-ethenopyrrolo[1'',2'':1',7']azepino[4',5':2,3]cyclopropa[1,2-*b*]indole-5-carboxylate ((±)-103)**



$BH_3{\cdot}SMe_2$ (190 µL, 2.01 mmol, 15 equiv) was added to a solution of (±)-**48** (49 mg, 0.134 mmol, 1 equiv) in anhydrous THF (1 mL) in a flame-dry 10 mL flask at 25 ºC, under argon atmosphere. The resulting colorless solution was stirred vigorously at 25 ºC for 2 h. A 4:1 mixture of methanol/formic acid (500 µL) was added in one portion at 0 ºC and stirring was continued at 25 ºC until no gas evolution was observed (*ca.* 30 min). The mixture was quenched with saturated aqueous $NaHCO_3$ and diluted with EtOAc (10 mL) and the pH of biphasic mixture was adjusted to ≥ 10 by addition of 6M aqueous NaOH. The organic layer was separated and the aqueous re-extracted with EtOAc (3 × 20 mL). The combined organic layers were dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude product was purified by preparative neutral aluminum oxide TLC eluting with EtOAc/cyclohexane 1 : 1 to afford (±)-**103** as a pale yellow oil (26.4 mg, 0.075 mmol, yield = 56%).

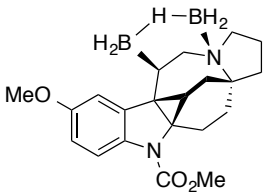
^{1}H NMR (500 MHz, $CDCl_3$, 298 K) δ 7.63 (d, *J* = 8.8 Hz, 1H), 6.76 (d, *J* = 2.6 Hz, 1H), 6.70 (dd, *J* = 8.8, 2.7 Hz, 1H), 6.37 (d, *J* = 10.2 Hz, 1H), 5.37 (dd, *J* = 10.2 Hz, 1H), 3.86 (s, 3H), 3.79 (s, 3H), 2.91 (ddd, *J* = 11.9, 9.1, 2.1 Hz, 1H), 2.84 – 2.67 (m, 3H), 2.60 (ddd, *J* = 15.3, 9.6, 3.0 Hz, 1H), 2.33 (d, *J* = 14.5 Hz, 1H), 2.23 (ddd, *J* = 15.4, 8.2, 2.1 Hz, 1H), 2.01 – 1.81 (m, 5H), 1.23 (dd, *J* = 4.6, 1.8 Hz, 1H). **^{13}C NMR** (126 MHz, $CDCl_3$, 328 K) δ 156.1, 154.7, 138.7, 135.2, 127.0, 126.7, 116.4, 111.9, 109.4, 59.8, 55.9, 54.7, 52.6, 51.2, 47.1, 41.5, 41.1, 29.0, 28.6, 22.6, 21.3. **HRMS** (ESI+) *m/z* calc. for $C_{21}H_{25}N_2O_3$ $[M+H]^+$: 353.1860, found: 353.1858.

(±)-Lundurine C from (±)-103

PtO_2 (0.7 mg, 0.031 mmol, 0.1 equiv) was placed in a dry flask and covered up with anhydrous methanol (1 mL) and the flask was placed under inert atmosphere. (±)-**103** (11 mg, 0.031 mmol, 1 equiv) was added and the mixture placed under 1 atm of hydrogen (2 sequences vacuum/hydrogen). It was then stirred vigorously at 25 ºC for 1.5 h. The solids were filtered off over Celite washing with dichloromethane and the

volatiles concentrated. 1H NMR analysis of the crude residue with 1,3-benzodioxole as internal standard showed 44% NMR yield of (±)-lundurine C (**3**).

6. Isolation of diborylated compound (±)-104



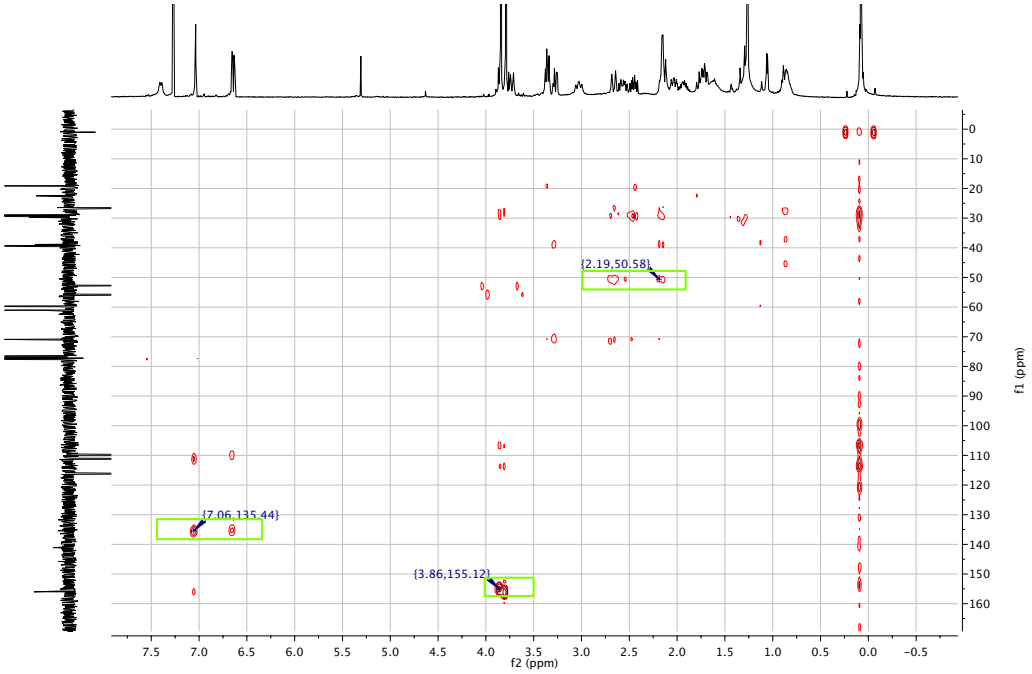
A 1M solution of $BH_3{\cdot}SMe_2$ in CH_2Cl_2 (430 µL, 0.43 mmol, 10 equiv) was added to solution of (±)-**97** (15.6 mg, 0.043 mmol, 1 equiv) in anhydrous THF (1 mL) in a flame-dry 10 mL flask at 25 ºC, under argon atmosphere. The resulting colorless solution was stirred vigorously at 60 ºC for 3 h. MeOH (200 µL) was added at 25 ºC and stirring was continued for 30 min at the same temperature. The volatiles were removed under vacuum and the crude mixture was purified by preparative silica gel TLC eluting with EtOAc/cyclohexane 1 : 1 to afford the title product as a white solid (14.1 mg, 0.037 mmol, yield = 87%). **M.p.** ≥ 180 ºC (slow melting and decomposition).

The structure of this compound was unambiguously confirmed by single crystal X-ray crystallography analysis (see below for more details). Solvent system for crystallization: dichloromethane, pentane.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.41 (d, *J* = 8.8 Hz, 1H), 7.04 (d, *J* = 2.7 Hz, 1H), 6.64 (dd, *J* = 8.8, 2.7 Hz, 1H), 3.84 (s, 3H), 3.79 (s, 3H), 3.73 (d, *J* = 12.5 Hz, 1H), 3.40 – 3.32 (m, 2H), 3.27 (dd, *J* = 12.5, 4.5 Hz, 1H), 3.08 – 2.97 (m, 1H), 2.70 – 2.63 (m, 1H), 2.57 (ddd, *J* = 14.9, 10.9, 8.1 Hz, 1H), 2.45 (ddd, *J* = 13.4, 11.7, 7.1 Hz, 1H), 2.20 – 1.87 (m, 5H), 1.80 – 1.67 (m, 2H), 1.06 (dd, *J* = 4.5, 1.6 Hz, 1H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 156.0, *155.1*, *135.4*, 116.0, 111.2, 110.0, 70.9, 61.0, 59.7, 55.7, 52.7, *50.6*, 39.3, 38.9, 29.2, 28.9, 26.5 (2C), 22.5, 19.1. *Note:* One quaternary carbon could not be detected; the signals between "*" were only observed or confirmed by 2D ^{13}C-^{1}H correlation (HMQC, HMBC), see below. **HRMS** (ESI+) *m/z* calc. for $C_{21}H_{30}B_2N_2O_3Na$ $[M+Na]^+$: 403.2335, found: 403.2343.

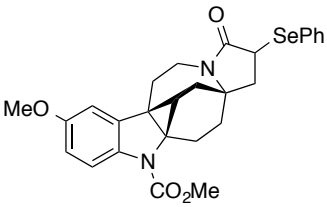
Note: the B–H signals could not be clearly observed as sharp signals in the ^{1}H NMR.

HMBC correlation for (±)-104:



7. Insaturation in lactam fragment

(±)-Methyl-2-methoxy-9-oxo-8-(phenylselanyl)-5b,6,8,9,11,12-hexahydro-5*H*,7*H*-5a,6a-ethanopyrrolo[1'',2'':1',7']azepino[4',5':2,3]cyclopropa[1,2-*b*]indole-5-carboxylate (107)

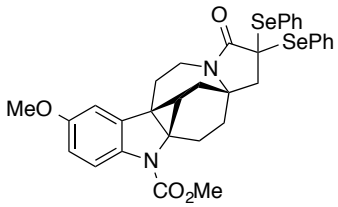


The solution of freshly prepared LDA (0.2 mL, 0.054 mmol, 2 equiv) was added to a solution of amide (±)-**105** (10 mg, 0.027 mmol, 1 equiv) in anhydrous THF (0.5 mL, if necessary use hot THF to dissolve) -78 ºC. After addition, the mixture was stirred for 30 min at -78 ºC and solution of PhSeBr (6.4 mg, 0.027 mmol, 1.05 equiv) in THF (0.2 mL) was added in one portion and the resulting mixture was stirred at -78 ºC for 1 h then Then the mixture was quenched by addition of saturated aqueous ammonium chloride (2 mL) and diluted CH_2Cl_2 (2 mL). The aqueous layer was re-extracted with CH_2Cl_2 (2 × 5 mL) and the combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification by silica gel preparative TLC eluting with EtOAc gave the title product as a colourless solid (4.2 mg, 0.008 mmol, yield = 30%) as well as diselenide **108** (6.1 mg, 0.011 mmol, yield =42 %).

M.p. (CH_2Cl_2/pentane) 78-89 ºC (decomposition).

The NMR characterization below corresponds to the mixture of this two diasteriomers in 65 : 35 ratio. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.74 – 7.63 (m, 2H *major* + 2H *minor*), 7.45 (br s, 1H *major* + 1H *minor*), 7.36 – 7.28 (m, 3H *major* + 3H *minor*), 6.72 (dd, *J* = 12.8, 2.6 Hz, 1H *major* + 1H *minor*), 6.66 (ddd, *J* = 8.8, 2.7, 1.6 Hz, 1H *major* + 1H *minor*), 4.16 (dt, *J* = 14.9, 4.5, 1H *major*), 4.04 (td, *J* = 9.4, 7.5 Hz, 1H *major* + 1H *minor*), 3.93 (ddd, *J* = 14.7, 6.0, 4.1 Hz, 1H *minor*), 3.85 (s, 3H *major*), 3.85 (s, 3H *minor*), 3.79 (s, 3H *major*), 3.78 (s, 3H *minor*), 3.63 (ddd, *J* = 14.3, 11.3, 2.8 Hz, 1H *minor*), 3.44 (ddd, *J* = 115.2, 12.4, 3.1 Hz, 1H *major*), 2.90 – 2.72 (m, 1H *major* + 1H *minor*), 2.70 – 2.38 (m, 3H *major* + 3H *minor*), 2.31 (ddd, *J* = 13.5, 9.0, 1.7 Hz, 1H *major* + 1H *minor*), 2.14 (m, 1H *major* + 2H *minor*), 2.07 (d, *J* = 3.8 Hz, 1H *major*), 1.96 (ddd, *J* = 13.5, 7.3, 2.7 Hz, 1H *major* + 1H *minor*), 1.87 – 1.76 (m, 1H *major* + 1H *minor*), 1.75 – 1.64 (m, 1H *major* + 1H *minor*), 1.03 (td, *J* = 4.5, 2.2 Hz, 1H *major* + 1H *minor*) . **^{13}C NMR** (126 MHz, $CDCl_3$) δ173.1, 172.6, 156.1, 156.0, 154.8 (2C), 139.3, 139.0, 135.3, 135.1 (2C), 135.1 (2C), 135.0, 129.1 (4C), 128.5, 128.4, 128.2, 128.2, 116.4 (2C), 111.3, 111.2, 109.1, 108.9, 60.3, 60.3, 55.8, 55.8, 52.3 (2C), 49.8, 49.6, 43.2, 42.9, 40.0, 39.9, 38.2, 37.3, 35.1, 33.9, 33.6, 33.5, 33.4, 33.0, 28.2, 27.3, 26.9, 26.8, 22.5, 22.2. **HRMS** (ESI+) *m/z* calc. for $C_{27}H_{29}N_2O_4S$^80Se$^+$ $[M+H]^+$: 525.1287, found: 525.1283.

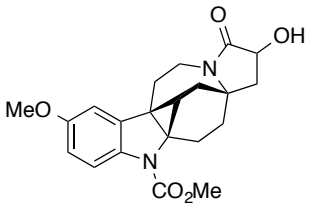
(±)-Methyl-2-methoxy-9-oxo-8,8-bis(phenylselanyl)-5b,6,8,9,11,12-hexahydro-5*H*,7*H*-5a,6a-ethanopyrrolo[1'',2'':1',7']azepino[4',5':2,3]cyclopropa[1,2-*b*]indole-5-carboxylate (108)



Yellow solid (6.7 mg, 0.01 mmol, yield = 37%).

M.p. (CH_2Cl_2/pentane) 95-105 ºC (decomposition). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.83 – 7.62 (m, 4H), 7.47 – 7.30 (m, 7H), 6.68 (dd, *J* = 2.6 Hz, 1H), 6.64 (dd, *J* = 8.8, 2.7, Hz, 1H), 4.20 − 4.07 (m, 1H), 3.81 (s, 3H), 3.78 (s, 3H), 3.35 (ddd, *J* = 15.3, 10.2, 5.7 Hz, 1H), 2.72 (dd, *J* = 15.5, 8.8 Hz, 1H), 2.56 – 2.37 (m, 3H), 2.20 – 2.07 (m, 2H), 1.77 (dd, *J* = 14.7, 5.5 Hz, 1H), 1.67 (d, *J* = 14.8 Hz, 1H), 1.50 (dd, *J* = 12.6, 9.3 Hz, 1H), 1.42 (dd, *J* = 14.0, 7.1 Hz, 1H), 0.87 (d, *J* = 4.6 Hz, 1H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ171.9, 156.1, 154.7, 139.2, 137.1 (2C), 137.1 (2C), 131.5, 129.5, 129.5, 129.2, 129.2, 129.1 (4C), 116.3, 111.1, 108.9, 60.3, 55.8, 52.3, 49.8, 42.9, 40.0, 39.9, 37.3, 33.6, 33.0, 28.2, 26.8, 22.5, **HRMS** (ESI+) *m/z* calc. for $C_{33}H_{33}N_2O_4$^80Se$_2^+$ $[M+H]^+$: 681.0765, found: 681.0771.

(±)-Methyl-8-hydroxy-2-methoxy-9-oxo-5b,6,8,9,11,12-hexahydro-5*H*,7*H*-5a,6a-ethanopyrrolo[1'',2'':1',7']azepino[4',5':2,3]cyclopropa[1,2-*b*]indole-5-carboxylate (109)



The solution of freshly prepared LDA (0.2 mL, 0.054 mmol, 2 equiv) was added to a solution of amide (±)-**105** (10 mg, 0.027 mmol, 1 equiv) in anhydrous THF (0.5 mL, if necessary use hot THF to dissolve) -78 ºC. After addition, the mixture was stirred for 30 min at -78 ºC and solution of Davis' oxazaridine (CSA-derived oxazaridine, 9.3 mg, 0.04 mmol, 1.5 equiv) in THF (0.2 mL) was added as a solution in anhydrous THF (0.5 mL) in one portion. The resulting mixture was stirred at -78 ºC for 2 h then -40 ºC for 1 h. The mixture was quenched by addition of saturated aqueous ammonium chloride (3 mL) and diluted CH_2Cl_2 (2 mL). The aqueous layer was re-extracted with CH_2Cl_2 (2 × 2 mL) and the combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. Purification by silica gel preparative TLC eluting with EtOAc gave the title product as a colourless solid as well as dicarbonyl **110**.

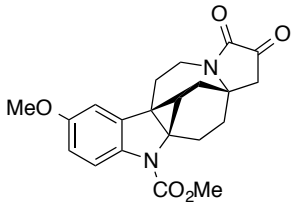
Note: 63% NMR yield of X (based on signal at 4.5 ppm), 1,3-benzodioxole as internal standard.

The structure of this compound was unambiguously confirmed by single crystal X-ray crystallography analysis (see below for more details). Solvent system for crystallization: nitromethane, ether, pentane. The melting point and NMR characterization below corresponds to the mixture of this two diasteriomers in 1 : 4 ratio.

M.p. (CH_2Cl_2/pentane) 216 - 220ºC (decomposition). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.48 (br s, 1H *major* + 1H *minor*), 6.79 (d, *J* = 2.6, 1H *major*), 6.71 – 6.65 (m, 1H *major* + 2H *minor*), 4.47 (m, 1H *major* + 1H *minor*), 4.18 (dt, *J* = 14.9, 4.2 Hz, 1H *minor*), 3.62 – 3.82 (m, 4H *major* + 3H *minor*), 3.79 (s, 3H *major*), 3.78 (s, 3H *minor*), 3.74 – 3.66 (m, 1H *major*), 3.43 (ddd, *J* = 15.5, 13.4, 3.1,1H *minor*), 3.30 (d, *J* = 2.6 Hz, 1H *minor*), 3.24 (d, *J* = 2.2 Hz, 1H *major*), 3.00 −2.92 (m, 1H *minor*), 2.81 – 2.61 (m, 2H *major* + 1H *minor*), 2.53 (dt, *J* = 14.9, 3.3 Hz, 1H *minor*), 2.45 – 2.10 (m, 5H *major* + 5H *minor*), 2.03 (m, 1H *minor*), 1.89 – 1.75 (m, 2H *major* + 1H *minor*), 1.71 (dd, *J* = 13.5, 6.2 Hz, 1H *major*), 1.10 (dd, *J* = 4.7, 1.9 Hz, 1H *major*), 1.06 (d, *J* = 5.1 Hz 1H *minor*). **^{13}C NMR** (126 MHz, $CDCl_3$) δ175.6, 173.4, 156.1, 156.0, 154.8, 154.8, 139.4,

138.5, 135.6, 135.3, 116.4 (2C), 111.6, 111.2, 109.3, 108.9, 69.1, 68.8, 58.9, 58.9, 55.8, 55.7, 52.9 (2C), 49.7, 49.0, 44.8, 44.1, 38.8, 36.2, 35.2, 33.7, 33.6, 33.3, 33.0, 32.9, 29.3, 38.8, 26.7, 26.6, 22.6, 21.4. **HRMS** (ESI+) *m/z* calc. for $C_{21}H_{24}N_2O_5Na^+$ $[M+Na]^+$: 407.1577, found: 407.1584.

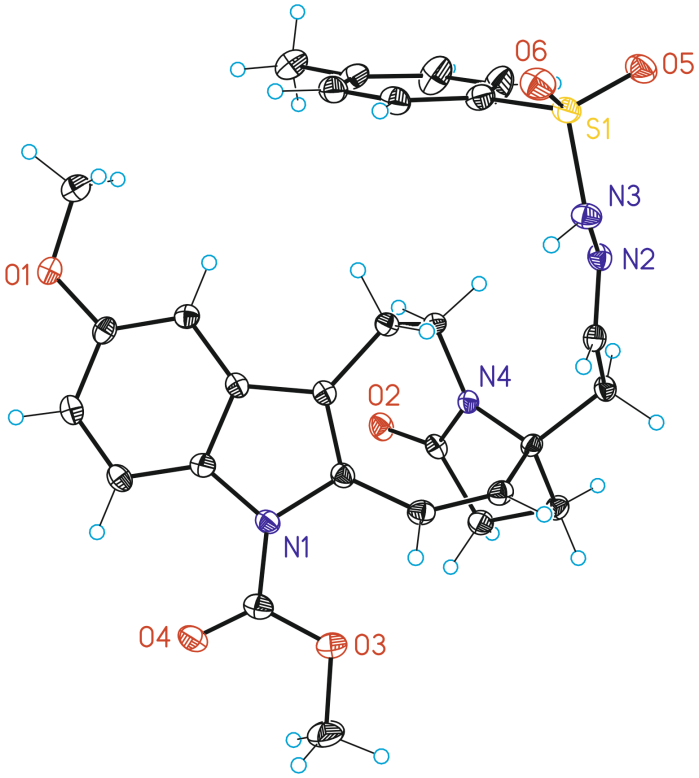
(±)-Methyl-2-methoxy-8,9-dioxo-5b,6,8,9,11,12-hexahydro-5*H*,7*H*-5a,6a-ethanopyrrolo[1'',2'':1',7']azepino[4',5':2,3]cyclopropa[1,2-*b*]indole-5-carboxylate (110)



^{1}H NMR (500 MHz, $CDCl_3$) δ 7.48 (br s, 1H), 6.75 (d, *J* = 2.6 Hz, 1H), 6.70 (dd, *J* = 8.8, 2.6 Hz, 1H), 4.35 (dt, *J* = 15.2, 4.6 Hz, 1H), 3.88 (s, 3H), 3.84 – 3.73 (m, 4H), 3.04 – 2.59 (m, 1H), 2.77 (ddd, *J* = 15.2, 4.6 Hz, 1H), 2.78 – 2.51 (m, 4H), 2.44 (dd, *J* = 14.9, 5.6 Hz, 1H), 2.26 (dd, *J* = 15.1, 2.2 Hz, 1H), 2.19 −2.05 (m, 1H), 1.80 (dd, *J* = 14.2, 6.4, 2.5 Hz, 1H), 1.16 (dd, *J* = 5.6, 1.1 Hz, 1H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 197.7, 159.5, 156.2, *154.8*, *138.5*, *135.2*, 116.5, 111.6, 109.0, 57.2, 55.8, 53.0, *49.0*, 48.3, 38.3, 35.2, 34.3, *33.4*, 27.7, 26.6, 22.4. **HRMS** (ESI+) *m/z* calc. for $C_{21}H_{22}N_2O_5Na^+$ $[M+Na]^+$: 405.1421, found: 405.1413. *Note:* The signals between "*" were only observed or confirmed by 2D ^{13}C-^{1}H correlation (HMQC, HMBC)

Crystallographic data:

Crystallographic data for compound (+)-96



ORTEP drawing with 50% probability of the thermal ellipsoids (one molecule of acetonitrile was omitted for clarity

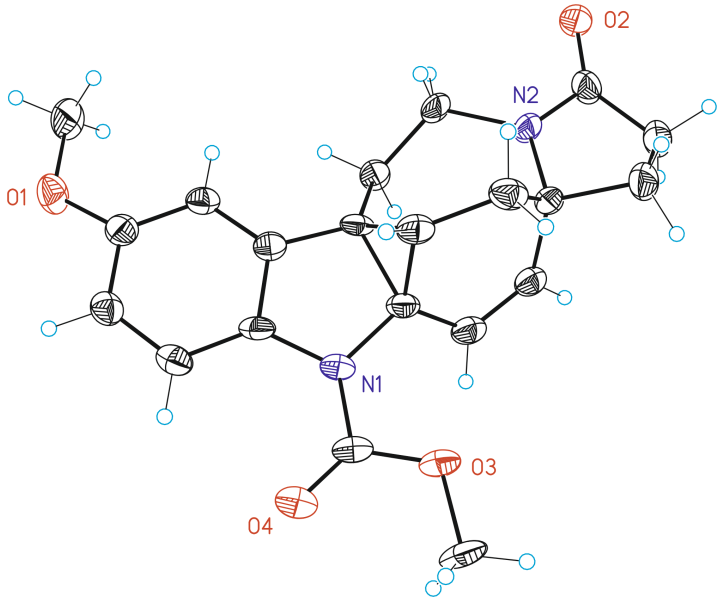
This CIF file was deposited with Cambridge Crystallographic Data Center: CCDC1448174

Table 1. Crystal data and structure refinement for mo_kms_L515_0m.

Identification code	mo_kms_L515_0m	
Empirical formula	C30 H33 N5 O6 S	
Formula weight	591.67	
Temperature	100(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P2(1)	
Unit cell dimensions	a = 9.7767(4)Å	a= 90°.
	b = 12.7913(6)Å	b = 90.2144(13)°.
	c = 11.7092(5)Å	g = 90°.
Volume	1464.30(11) Å^3	

Z	2
Density (calculated)	1.342 Mg/m^3
Absorption coefficient	0.163 mm^{-1}
F(000)	624
Crystal size	0.35 x 0.15 x 0.10 mm^3
Theta range for data collection	2.083 to 30.587°.
Index ranges	-13<=h<=13,-17<=k<=18,-16<=l<=10
Reflections collected	21001
Independent reflections	8464[R(int) = 0.0243]
Completeness to theta =30.587°	99.7%
Absorption correction	Multi-scan
Max. and min. transmission	0.984 and 0.929
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	8464/ 2/ 386
Goodness-of-fit on F^2	1.042
Final R indices [I>2sigma(I)]	R1 = 0.0352, wR2 = 0.0848
R indices (all data)	R1 = 0.0394, wR2 = 0.0873
Flack parameter	x =0.03(2)
Largest diff. peak and hole	0.484 and -0.287 $e.Å^{-3}$

Crystallographic data for compound (±)-48



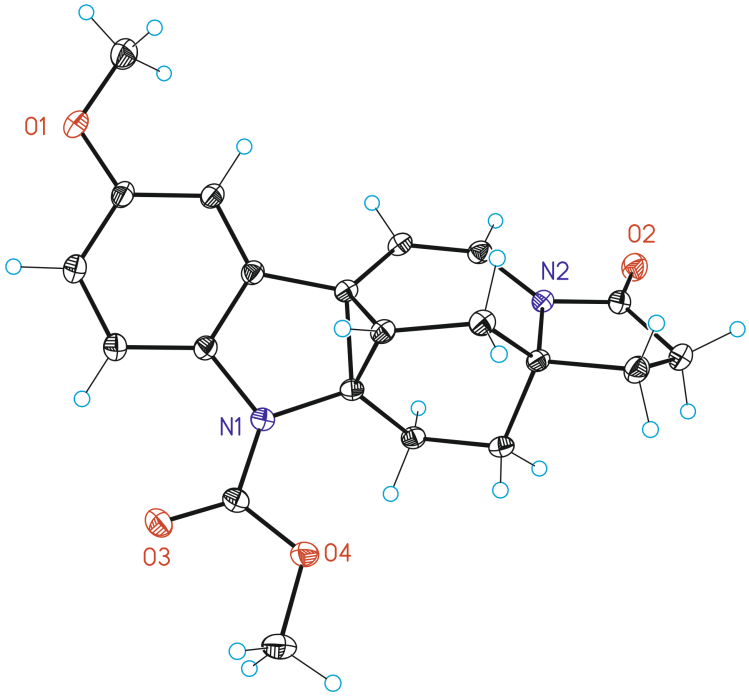
ORTEP drawing with 50% probability of the thermal ellipsoids (the compound was disordered and one of the two conformers was omitted for clarity)

This CIF file was deposited with Cambridge Crystallographic Data Center: CCDC1448178

Table 1. Crystal data and structure refinement for mo_KMS_L595_0m.

Identification code	mo_KMS_L595_0m	
Empirical formula	C21 H22 N2 O4	
Formula weight	366.40	
Temperature	100(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P2(1)/c	
Unit cell dimensions	a = 15.0036(12)Å	a= 90°.
	b = 8.2237(6)Å	b = 103.354(3)°.
	c = 14.9928(12)Å	g = 90°.
Volume	1799.9(2) $Å^3$	
Z	4	
Density (calculated)	1.352 Mg/m^3	
Absorption coefficient	0.094 mm^{-1}	
F(000)	776	
Crystal size	0.30 x 0.20 x 0.06 mm^3	
Theta range for data collection	1.395 to 28.525°.	
Index ranges	-20<=h<=18,-11<=k<=10,-12<=l<=20	
Reflections collected	14351	
Independent reflections	4498[R(int) = 0.0274]	
Completeness to theta =28.525°	98.7%	
Absorption correction	Multi-scan	
Max. and min. transmission	0.994 and 0.945	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	4498/ 569/ 491	
Goodness-of-fit on F^2	1.173	
Final R indices [I>2sigma(I)]	R1 = 0.0495, wR2 = 0.1551	
R indices (all data)	R1 = 0.0710, wR2 = 0.1728	
Largest diff. peak and hole	0.210 and -0.215 e.$Å^{-3}$	

Crystallographic data for compound (–)-97



ORTEP drawing with 50% probability of the thermal ellipsoids (the compound was disordered and one of the two conformers was omitted for clarity)

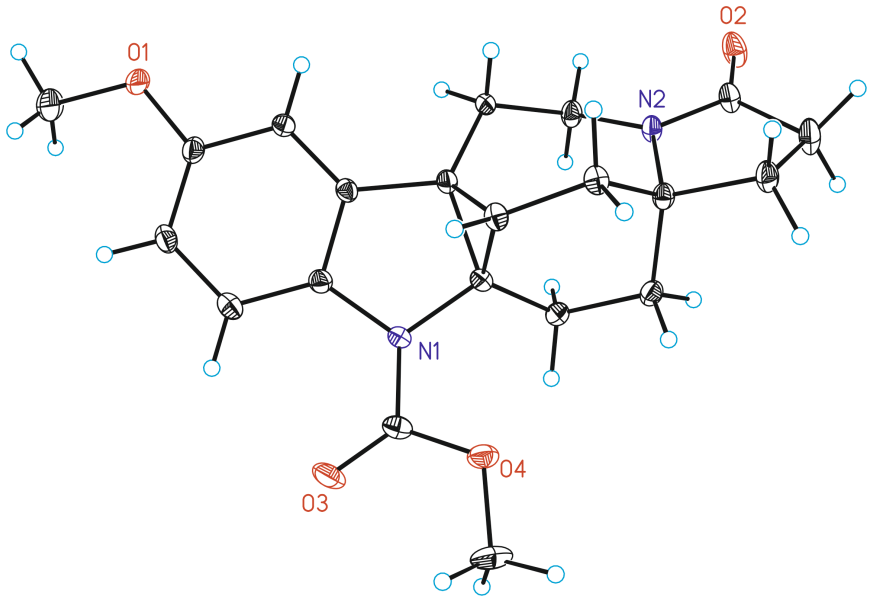
This CIF file was deposited with Cambridge Crystallographic Data Center: CCDC1448176

Table 1. Crystal data and structure refinement for KMS-L588b.

Identification code	KMS-L588b	
Empirical formula	C21 H22 N2 O4	
Formula weight	366.40	
Temperature	100(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P2(1)	
Unit cell dimensions	a = 6.90752(9)Å	a= 90°.
	b = 7.97355(9)Å	b = 100.4059(12)°.
	c = 15.9186(2)Å	g = 90°.
Volume	862.335(19) $Å^3$	
Z	2	
Density (calculated)	1.411 Mg/m^3	
Absorption coefficient	0.098 mm^{-1}	
F(000)	388	

Crystal size	? x ? x ? mm^3
Theta range for data collection	2.602 to 62.171°.
Index ranges	-16<=h<=16,-19<=k<=19,-39<=l<=39
Reflections collected	132011
Independent reflections	26545[R(int) = 0.0446]
Completeness to theta =62.171°	97.299995%
Absorption correction	Multi-scan
Max. and min. transmission	0.993 and 0.764
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	26545/ 634/ 492
Goodness-of-fit on F^2	1.024
Final R indices [I>2sigma(I)]	R1 = 0.0286, wR2 = 0.0825
R indices (all data)	R1 = 0.0331, wR2 = 0.0849
Flack parameter	x =0.00(8)
Largest diff. peak and hole	0.480 and -0.222 e.$Å^{-3}$

Crystallographic data for compound (±)-105



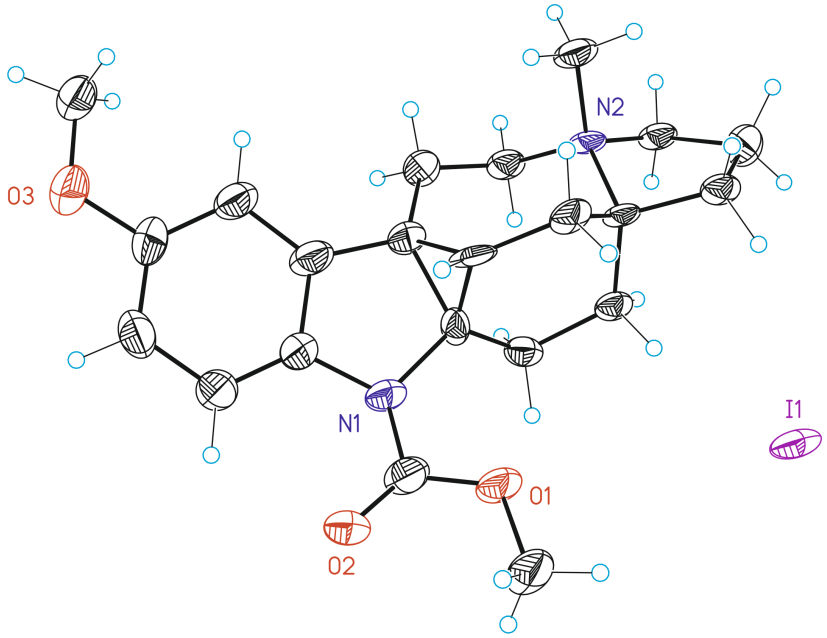
ORTEP drawing with 50% probability of the thermal ellipsoids

This CIF file was deposited with Cambridge Crystallographic Data Center: CCDC1448172

Table 1. Crystal data and structure refinement for mo_KMS_L612_0m.

Identification code	mo_KMS_L612_0m	
Empirical formula	C21 H24 N2 O4	
Formula weight	368.42	
Temperature	100(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P2(1)/c	
Unit cell dimensions	a = 6.9148(3)Å	a= 90°.
	b = 12.6392(5)Å	b = 92.3940(14)°.
	c = 20.2868(9)Å	g = 90°.
Volume	1771.47(13) $Å^3$	
Z	4	
Density (calculated)	1.381 Mg/m^3	
Absorption coefficient	0.096 mm^{-1}	
F(000)	784	
Crystal size	0.51 x 0.30 x 0.12 mm^3	
Theta range for data collection	2.576 to 31.881°.	
Index ranges	-7<=h<=10,-16<=k<=18,-26<=l<=30	
Reflections collected	18948	
Independent reflections	5563[R(int) = 0.0308]	
Completeness to theta =31.881°	91.2%	
Absorption correction	Empirical	
Max. and min. transmission	0.989 and 0.953	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	5563/ 0/ 246	
Goodness-of-fit on F^2	1.050	
Final R indices [I>2sigma(I)]	R1 = 0.0471, wR2 = 0.1183	
R indices (all data)	R1 = 0.0601, wR2 = 0.1280	
Largest diff. peak and hole	0.430 and -0.434 e.$Å^{-3}$	

Crystallographic data for compound 106



ORTEP drawing with 50% probability of the thermal ellipsoids, only one rotamer represented

This CIF file was deposited with Cambridge Crystallographic Data Center: CCDC1448177

The asymmetric unit contained one molecule of the iodide salt. The methyl group of the ether residue was disordered in two orientations (ratio 90:10). The measured sample consisted of two crystals in 52:48 ratio. The collected data for both crystals were processed with TWINABS taking into account overlapping reflections.[61]

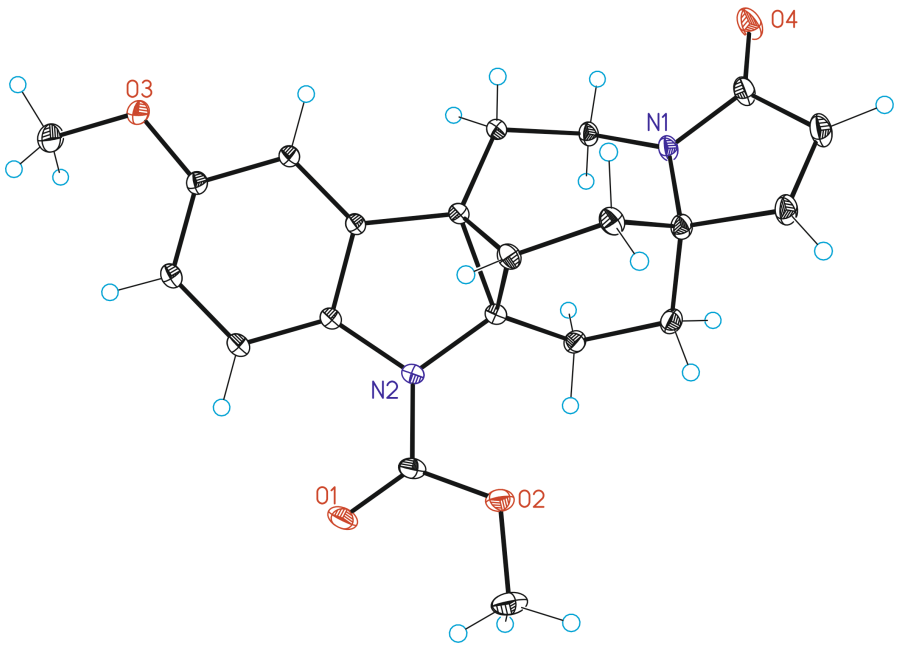
Table 1. Crystal data and structure refinement for mo_KMS_L593b_05.

Identification code	mo_KMS_L593b_05	
Empirical formula	C22 H28 I N2 O3	
Formula weight	495.36	
Temperature	100(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P2(1)	
Unit cell dimensions	a = 10.2983(9)Å	a= 90°.
	b = 8.8605(8)Å	b = 93.010(3)°.
	c = 12.0623(11)Å	g = 90°.

[61] Blessing, R. H., *Acta Cryst*. **1995,** *A51*, 33-38.

Volume	1099.14(17) $Å^3$
Z	2
Density (calculated)	1.497 Mg/m^3
Absorption coefficient	1.481 mm^{-1}
F(000)	502
Crystal size	0.25 x 0.10 x 0.05 mm^3
Theta range for data collection	1.691 to 28.106°.
Index ranges	-13<=h<=13,-11<=k<=11,-15<=l<=15
Reflections collected	7481
Independent reflections	7481[R(int) = ?]
Completeness to theta =28.106°	100.0%
Absorption correction	Empirical
Max. and min. transmission	0.930 and 0.438
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	7481/ 89/ 265
Goodness-of-fit on F^2	1.028
Final R indices [I>2sigma(I)]	R1 = 0.0799, wR2 = 0.1985
R indices (all data)	R1 = 0.0943, wR2 = 0.2103
Flack parameter	x =-0.04(4)
Largest diff. peak and hole	2.847 and -1.975 $e.Å^{-3}$

Crystallographic data for compound (–)-1 (enantiopure lundurine A)



ORTEP drawing with 50% probability of the thermal ellipsoids

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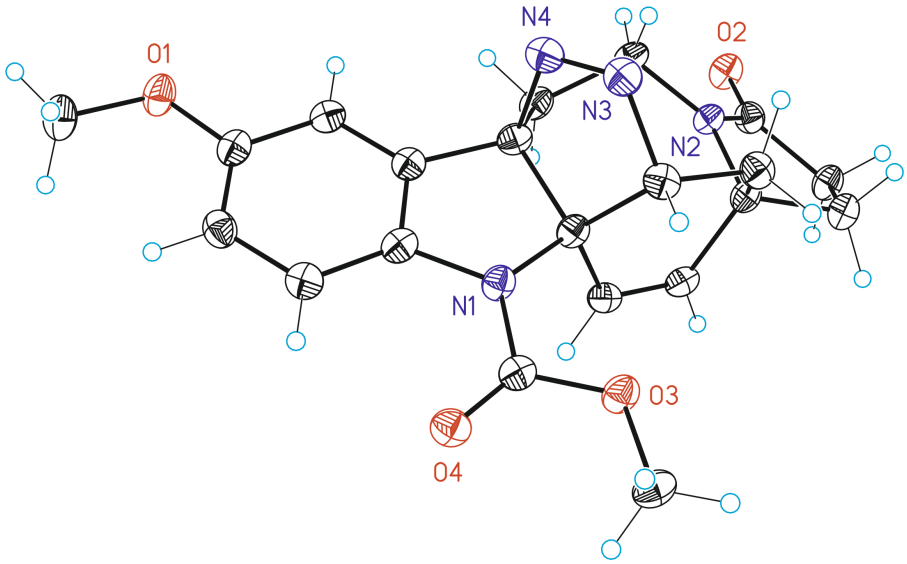
Table 1. Crystal data and structure refinement for MMu1213_b.

Identification code	MMu1213_b	
Empirical formula	C21 H22 N2 O4	
Formula weight	366.40	
Temperature	100(2) K	
Wavelength	0.71073 Å	
Crystal system	orthorhombic	
Space group	P 21 21 2	
Unit cell dimensions	a = 20.6494(3)Å	a= 90°.
	b = 12.6339(2)Å	b = 90°.
	c = 6.81766(11)Å	g = 90°.
Volume	1778.60(5) $Å^3$	
Z	4	
Density (calculated)	1.368 Mg/m^3	
Absorption coefficient	0.095 mm^{-1}	
F(000)	776	
Crystal size	0.2 x 0.05 x 0.05 mm^3	
Theta range for data collection	1.890 to 62.116°.	
Index ranges	-46<=h<=50,-25<=k<=26,-15<=l<=14	
Reflections collected	81263	
Independent reflections	21428[R(int) = 0.0240]	
Completeness to theta =62.116°	84.0%	
Absorption correction	Multi-scan	
Max. and min. transmission	0.995 and 0.765	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	21428/ 0/ 246	
Goodness-of-fit on F^2	1.044	
Final R indices [I>2sigma(I)]	R1 = 0.0316, wR2 = 0.0879	
R indices (all data)	R1 = 0.0385, wR2 = 0.0912	
Flack parameter	x =-0.08(8)	
Largest diff. peak and hole	0.495 and -0.246 e.$Å^{-3}$	

Crystallographic data for compound (±)-100



ORTEP drawing with 50% probability of the thermal ellipsoids (one molecule of water was omitted for clarity)

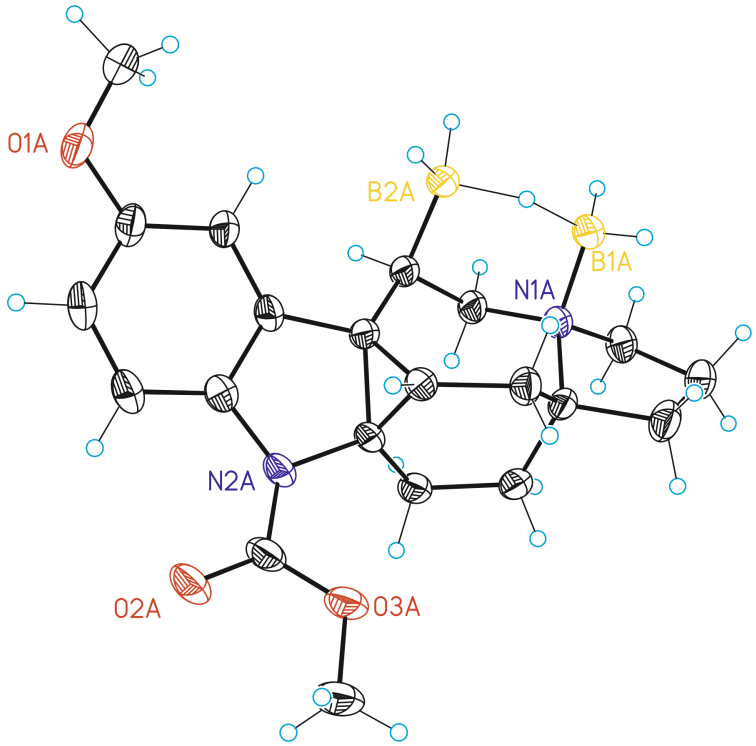
This CIF file was deposited with Cambridge Crystallographic Data Center: CCDC1448175

Table 1. Crystal data and structure refinement for mo_KMS_L568_05.

Identification code	mo_KMS_L568_05	
Empirical formula	C21 H24 N4 O5	
Formula weight	412.44	
Temperature	100(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P2(1)/c	
Unit cell dimensions	a = 21.910(8)Å	a= 90°.
	b = 7.3949(15)Å	b = 93.859(13)°.
	c = 11.738(2)Å	g = 90°.
Volume	1897.6(9) $Å^3$	
Z	4	
Density (calculated)	1.444 Mg/m^3	
Absorption coefficient	0.105 mm^{-1}	
F(000)	872	
Crystal size	0.10 x 0.05 x 0.02 mm^3	
Theta range for data collection	0.931 to 27.541°.	
Index ranges	-28<=h<=28,0<=k<=9,0<=l<=15	

Reflections collected	9290
Independent reflections	9290[R(int) = ?]
Completeness to theta =27.541°	99.5%
Absorption correction	Multi-scan
Max. and min. transmission	0.998 and 0.768
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	9290/ 3/ 280
Goodness-of-fit on F^2	1.136
Final R indices [I>2sigma(I)]	R1 = 0.0624, wR2 = 0.1678
R indices (all data)	R1 = 0.0954, wR2 = 0.1873
Largest diff. peak and hole	0.480 and -0.272 e.$Å^{-3}$

Crystallographic data for compound (±)-104



ORTEP drawing with 50% probability of the thermal ellipsoids – only one rotamer represented (crystallizes as a mixture of MeO/CO_2Me rotamers)

This CIF file was deposited with Cambridge Crystallographic Data Center: CCDC1448173

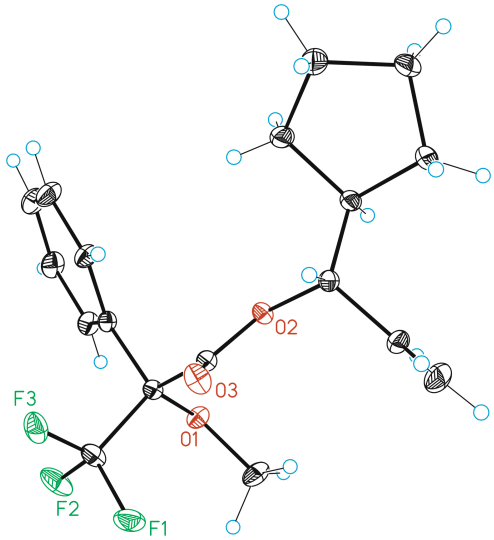
Table 1. Crystal data and structure refinement for mo_KMS_L501b_0m.

Identification code	mo_KMS_L501b_0m
Empirical formula	C21 H30 B2 N2 O3

Chapter 2. Total Synthesis of Lundurines A−C

Formula weight	380.09	
Temperature	100(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P2(1)/n	
Unit cell dimensions	a = 9.6622(9)Å	⟨= 90°.
	b = 36.388(4)Å	® = 112.866(3)°.
	c = 12.3024(11)Å	© = 90°.
Volume	3985.5(7) $Å^3$	
Z	8	
Density (calculated)	1.267 Mg/m^3	
Absorption coefficient	0.082 mm^{-1}	
F(000)	1632	
Crystal size	0.30 x 0.10 x 0.06 mm^3	
Theta range for data collection	1.679 to 28.962°.	
Index ranges	-9<=h<=12,-49<=k<=46,-16<=l<=16	
Reflections collected	34799	
Independent reflections	10444[R(int) = 0.0611]	
Completeness to theta =28.962°	98.7%	
Absorption correction	Empirical	
Max. and min. transmission	0.995 and 0.754	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	10444/ 96/ 577	
Goodness-of-fit on F^2	1.055	
Final R indices [I>2sigma(I)]	R1 = 0.0806, wR2 = 0.2203	
R indices (all data)	R1 = 0.0975, wR2 = 0.2445	
Largest diff. peak and hole	0.361 and -0.479 $e.Å^{-3}$	

Crystallographic data for compound (*S*,*S*)-80f



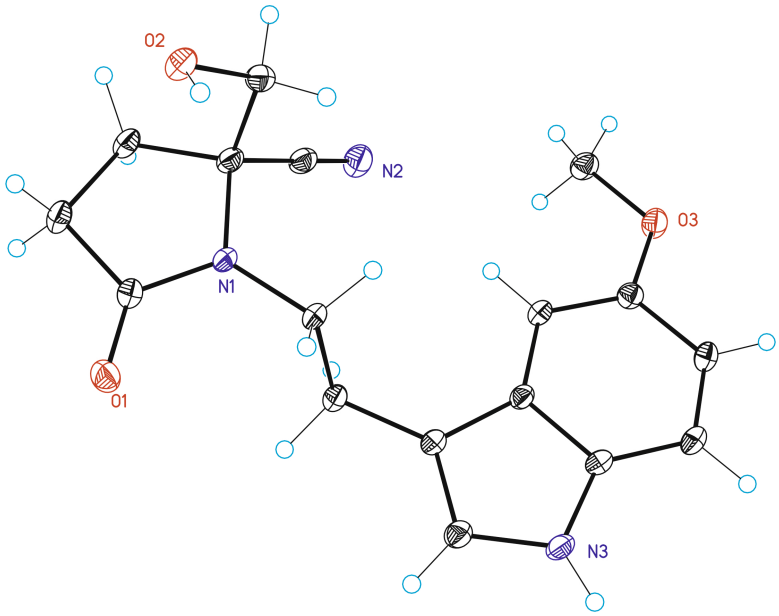
This CIF file was deposited with Cambridge Crystallographic Data Center: CCDC1462878

Table 1. Crystal data and structure refinement for MMu1224S_b.

Identification code	MMu1224S_b	
Empirical formula	C18 H21 F3 O3	
Formula weight	342.35	
Temperature	100(2) K	
Wavelength	0.71073 Å	
Crystal system	Orthorhombic	
Space group	P2(1)2(1)2(1)	
Unit cell dimensions	a = 8.64457(5)Å	⟨= 90°.
	b = 11.59041(7)Å	® = 90°.
	c = 17.25771(9)Å	© = 90°.
Volume	1729.122(17) Å^3	
Z	4	
Density (calculated)	1.315 Mg/m^3	
Absorption coefficient	0.108 mm^{-1}	
F(000)	720	
Crystal size	0.3 x 0.25 x 0.2 mm^3	
Theta range for data collection	2.117 to 62.377°.	
Index ranges	-21<=h<=21,-28<=k<=28,-42<=l<=42	
Reflections collected	317715	
Independent reflections	27723[R(int) = 0.0290]	
Completeness to theta =62.377°	99.3%	

Absorption correction	Multi-scan
Max. and min. transmission	0.979 and 0.753
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	27723/ 0/ 301
Goodness-of-fit on F^2	1.101
Final R indices [I>2sigma(I)]	R1 = 0.0241, wR2 = 0.0703
R indices (all data)	R1 = 0.0254, wR2 = 0.0711
Flack parameter	x =-0.002(17)
Largest diff. peak and hole	0.534 and -0.294 e.$Å^{-3}$

Crystallographic data for compound (±)-55



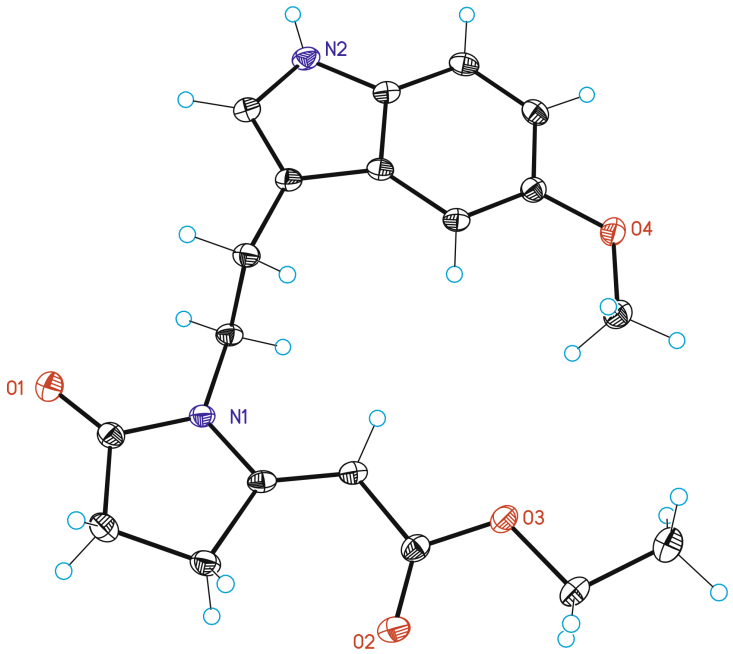
This CIF file was deposited with Cambridge Crystallographic Data Center: CCDC145477

Table 1. Crystal data and structure refinement for mo_kms_L50_0m.

Identification code	mo_kms_L50_0m	
Empirical formula	C17 H19 N3 O3	
Formula weight	313.35	
Temperature	100(2) K	
Wavelength	0.71073 Å	
Crystal system	Triclinic	
Space group	P-1	
Unit cell dimensions	a = 7.7467(4) Å	a= 101.655(2) °.

	b = 8.3299(4) Å	b = 93.023(2) °.
	c = 12.0072(6) Å	g = 93.877(2) °.
Volume	755.35(7) Å^3	
Z	2	
Density (calculated)	1.378 Mg/m^3	
Absorption coefficient	0.096 mm^{-1}	
F(000)	332	
Crystal size	0.30 x 0.25 x 0.15 mm^3	
Theta range for data collection	1.74 to 30.23 °.	
Index ranges	-10 <=h<=10 ,-11 <=k<=10 ,-16 <=l<=16	
Reflections collected	9263	
Independent reflections	3947 [R(int) = 0.0217]	
Completeness to theta =30.23 °	87.9%	
Absorption correction	Empirical	
Max. and min. transmission	0.9857 and 0.9717	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	3947 / 0 / 210	
Goodness-of-fit on F^2	1.059	
Final R indices [I>2sigma(I)]	R1 = 0.0413 , wR2 = 0.1099	
R indices (all data)	R1 = 0.0447 , wR2 = 0.1129	
Largest diff. peak and hole	0.489 and -0.435 e.Å^{-3}	

Crystallographic data for compound (±)-72



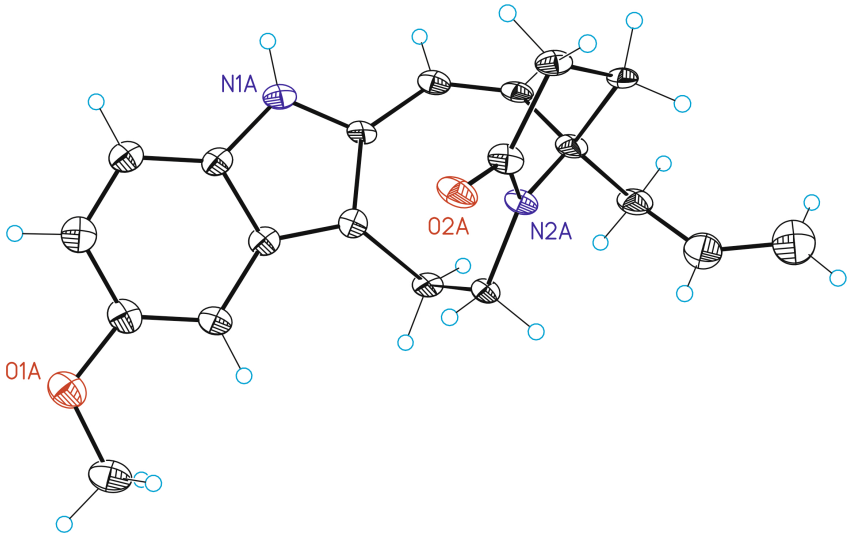
Chapter 2. Total Synthesis of Lundurines A−C

This CIF file was deposited with Cambridge Crystallographic Data Center: CCDC1454178

Table 1. Crystal data and structure refinement for mo_KMS_L108_1_0m.

Identification code	mo_KMS_L108_1_0m	
Empirical formula	C19 H22 N2 O4	
Formula weight	342.39	
Temperature	100(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P2(1)/n	
Unit cell dimensions	a = 10.1237(5) Å	a= 90.00 °.
	b = 8.9706(4) Å	b = 100.3640(10) °.
	c = 18.7023(8) Å	g = 90.00 °.
Volume	1670.75(13) $Å^3$	
Z	4	
Density (calculated)	1.361 Mg/m^3	
Absorption coefficient	0.096 mm^{-1}	
F(000)	728	
Crystal size	0.40 x 0.30 x 0.20 mm^3	
Theta range for data collection	2.14 to 30.48 °.	
Index ranges	-14 <=h<=13 ,-10 <=k<=12 ,-26 <=l<=26	
Reflections collected	34402	
Independent reflections	4618 [R(int) = 0.0235]	
Completeness to theta =30.48 °	90.7%	
Absorption correction	Empirical	
Max. and min. transmission	0.9810 and 0.9626	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	4618 / 0 / 232	
Goodness-of-fit on F^2	1.033	
Final R indices [I>2sigma(I)]	R1 = 0.0397 , wR2 = 0.1061	
R indices (all data)	R1 = 0.0447 , wR2 = 0.1107	
Largest diff. peak and hole	0.429 and -0.274 $e.Å^{-3}$	

Crystallographic data for compound (±)-93a



This CIF file was deposited with Cambridge Crystallographic Data Center: CCDC1454180

Table 1. Crystal data and structure refinement for RD-L032.

Identification code	RD-L032	
Empirical formula	C20.50 H22.50 Cl1.50 N2 O2	
Formula weight	382.08	
Temperature	100(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P2(1)/n	
Unit cell dimensions	a = 10.740(2)Å	a= 90°.
	b = 25.466(6)Å	b = 90.047(5)°.
	c = 28.178(7)Å	g = 90°.
Volume	7707(3) $Å^3$	
Z	16	
Density (calculated)	1.317 Mg/m^3	
Absorption coefficient	0.285 mm^{-1}	
F(000)	3216	
Crystal size	0.20 x 0.20 x 0.20 mm^3	
Theta range for data collection	2.058 to 25.412°.	
Index ranges	-12<=h<=12,-25<=k<=30,-33<=l<=33	
Reflections collected	60987	
Independent reflections	14165[R(int) = 0.1431]	
Completeness to theta =25.412°	99.8%	

Absorption correction	Multi-scan
Max. and min. transmission	0.945 and 0.727
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	14165/ 1410/ 1267
Goodness-of-fit on F^2	0.920
Final R indices [I>2sigma(I)]	R1 = 0.0915, wR2 = 0.2252
R indices (all data)	R1 = 0.1918, wR2 = 0.2652
Largest diff. peak and hole	0.967 and -0.525 e.Å^{-3}